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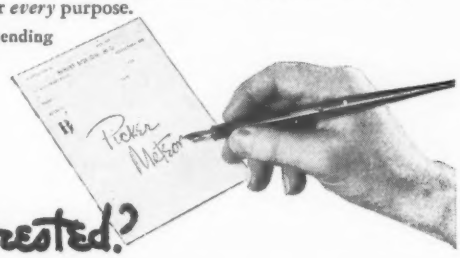

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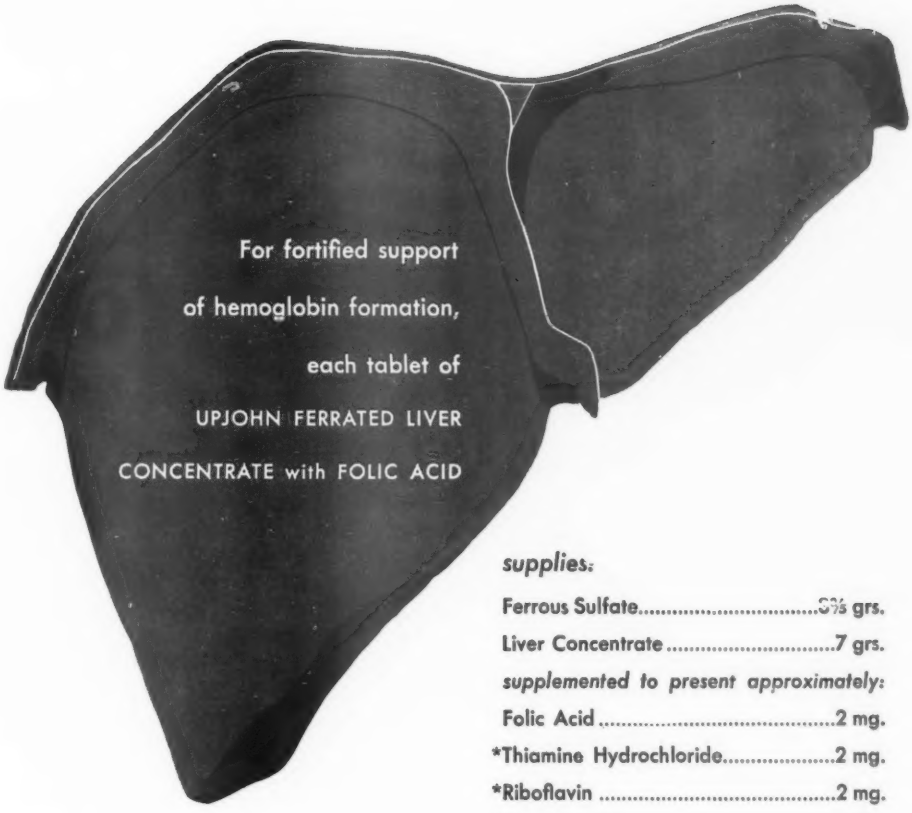

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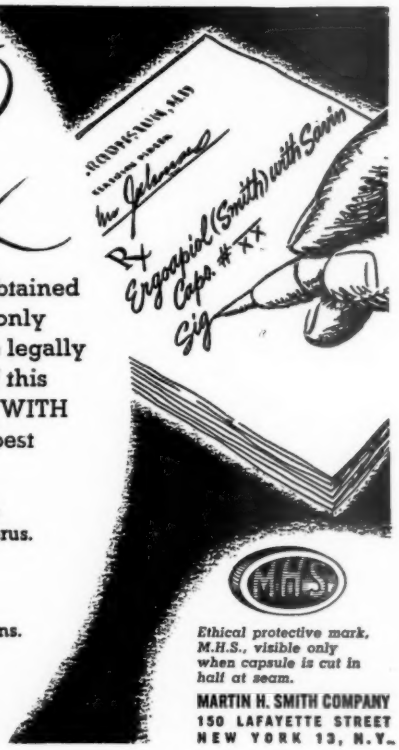

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1. Lennox, M. A. (1948), Drug Treatment of Epilepsy Connecticut State Med. J., 12:1006, November.

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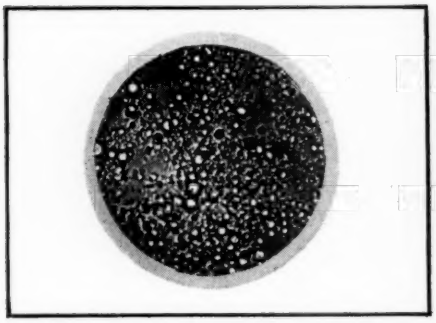

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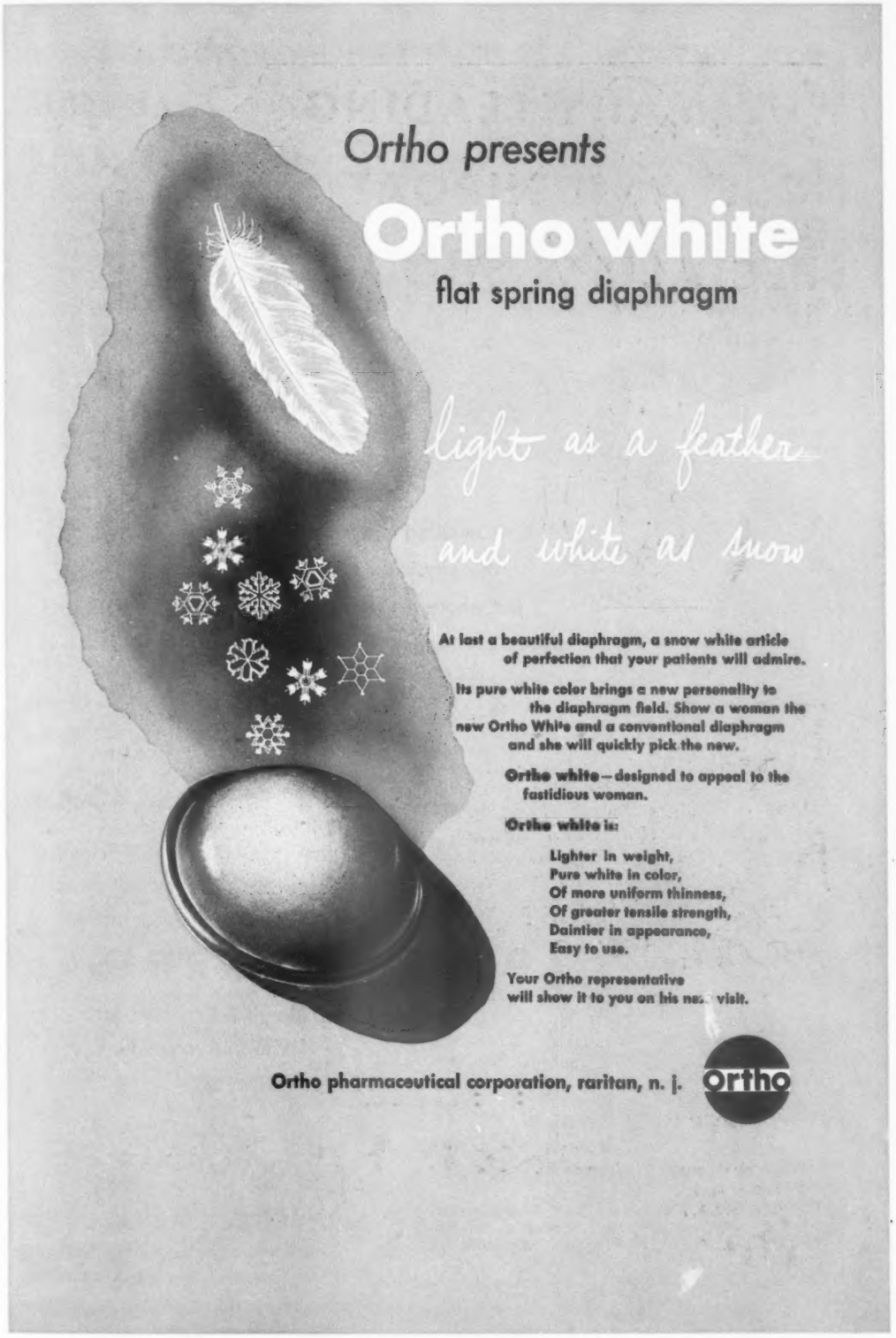
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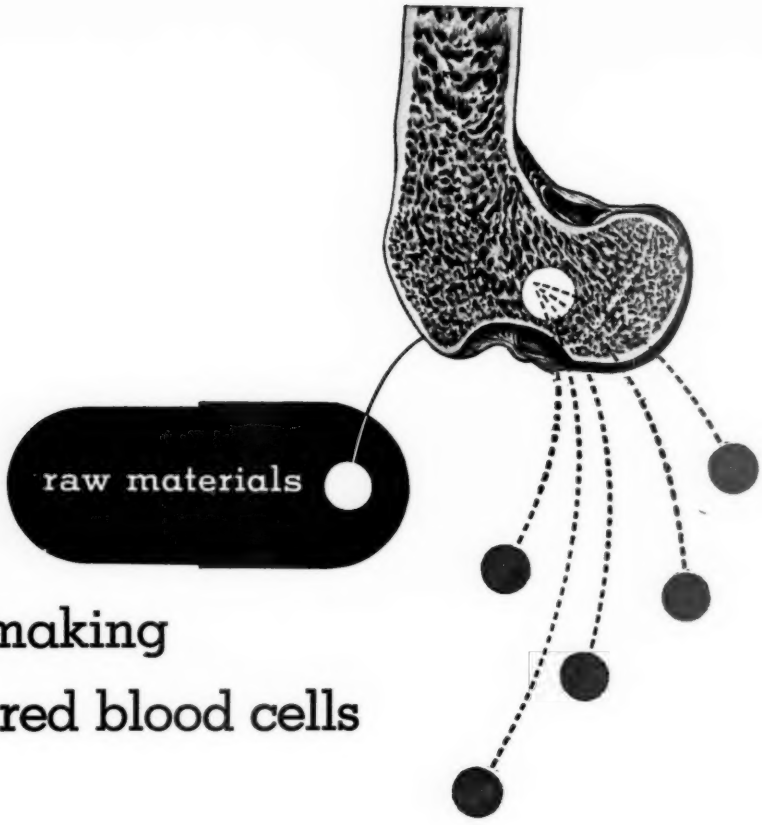

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The Reticulo—Endothelial System

Edna H. Tompkins, M. D.

Origin and Interrelationships of the Cells of the R-E System

The term reticulo-endothelial system will be abbreviated to R-E throughout. It is used to designate the phagocytic mononuclear cells that occur as either fixed or free forms in the connective tissues throughout the body, in the interstitial tissues of all parenchymatous organs, and in all sinusoidal areas. It is a term which arose out of a long polemic which has not yet been concluded and which concerned the origin, variety, and interrelationships of the various cells of the system. Those cells about which there is no longer controversy as to their inclusion in the system comprise: the monocytes of the blood; the large mononuclear phagocytes of normal connective tissues, i.e., histiocytes; the free large mononuclear phagocytes of inflammatory areas and of the parenchymatous organs, such as the spleen and lymph nodes, i.e., the macrophages, or clasmatocytes; the endothelial cells which line blood and lymph sinusoids, i.e., the so-called "specific endothelium," including the Kupffer cells of the liver; and the reticular cells in the supportive tissues of parenchymatous organs which lie along the smaller nerves and blood and lymph vessels. The peripheral reticulo-endothelial cells which Neukomm[37] has recently described seem to be monocytes.

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Whether the fibroblasts of connective tissues, the lymphocytes of the hematopoietic organs, and the microglial cells of the nervous system should be included as integral parts of the system remains controversial.

Although the presence of motile cells capable of phagocytosis was recognized earlier, description and classification of them and detailed studies of their physiology were first recorded by Metchnikoff.[34] He was concerned largely with the cells which enter areas of inflammation, and he classified those into the microphages and the macrophages. His contributions concerning the physiologic capacities of the latter, and his findings or suppositions as to their biologic significance in the defense and immune reactions of the body represent a preview of most of the studies on the R-E system that have accumulated since his time.

Metchnikoff's investigations were broad and general and pioneer. They naturally led to a series of more specific and limited studies, resulting in discovery of the various other cells of the R-E system which have lesser, or equal, phagocytic capacity of those of the macrophages which Metchnikoff studied. From these latter contributions there arose extensive controversies as to the origin, specificity, or interrelationships of the various phagocytic cells of the body. These controversies have lessened, although few of them were answered definitively, and workers in the field have turned their attention in recent years to studies of the normal and pathologic activities of the system and to the significance and utilization of those activities for the defenses of the body.

The many studies centering about the origin and relationships of the various cells of the R-E system have been exhaustively reviewed on numerous occasions. The review by Jaffé[26] in 1938 contains an extensive bibliography. Effort here will be directed toward outline and discussion of those

concepts that are still controversial and of which persons interested in the field should be cognizant, rather than toward further detailed presentation of the contributions that support or refute any given concept. It seems important to be aware of the points of controversy, and of those concepts about the cells of the system which represent hypotheses rather than proven facts, in order that new data concerning the system may be properly evaluated, and also in order that controversial points may be terminated whenever new data permit.

One of the methods which Metchnikoff employed consisted of the use of a dye which the macrophages could phagocytose and segregate without immediate injury to their physiologic activities. He found that weak solutions of neutral red in the tissue fluids were suitable for this purpose. Sabin, who had had the opportunity to work in his laboratory, introduced the technique into this country. Together with her collaborators,[11, 45] she defined the free cells of the R-E system morphologically, and demonstrated that the cells of the blood designated as large mononuclear and transitional cells are one and the same cell in various stages of activity. They called this cell the monocyte. They demonstrated that normal connective tissues contain two types of free, large mononuclear, phagocytic cells, the monocyte and the clasmatocyte, and that both are present within the reticulum of the various blood-forming organs.

Sabin and her collaborators believe that monocytes and clasmatocytes, i.e., macrophages, represent definitive and unrelated cells. This belief led to a long standing controversy. Those working with inflamed tissues and tissue cultures came to the contrary conclusion, namely, that the two cells are merely different physiologic states of a single cell, i.e., that the macrophage represents a more actively phagocytic state of the monocyte. The studies of Bloom[8] in inflammation, those of the Lewises[32] and others with tissue cultures, and those of Tompkins[55, 57] following subcutaneous injections of specific lipids all seem to support this concept. At any rate, it has now become rather generally accepted by the more recent workers in the R-E system that monocytes may become macrophages if their phagocytic activity is sufficiently stimulated and that, moreover, many of the macrophages found about areas of inflammation or in the organs normally have arisen from preceding monocytes.

This controversy, however, leads to a related one that cannot be answered so definitely. In non-inflamed normal connective tissues, clusters of actively phagocytic cells occur that are elongated and apparently immobile. These are called histiocytes by Kiyono,[29] clasmatocytes by Ranvier,[41] and resting wandering cells by Maximow.[33] Kiyono's use of the term histiocyte actually includes monocytes, but present usage of the term has come to be limited as indicated here. These cells differ morphologically in certain respects from the rounded, mobile macrophages that characterize areas of inflammation and that are found free in the supportive tissues of the organs. They disappear during inflammation and only macrophages occur. The argument naturally arises as to how they are related to the macrophages that enter the tissues in inflammation and to the free mononuclear phagocytes of the organs, which are morphologically similar to the macrophages of inflammation.

The answer to these questions was sought by two experimental approaches: (1) production of experimental inflammatory reactions in connective tissues in order to correlate the succeeding transformations in the histiocytes and in the cells that entered from the blood; and (2) vital staining of animals with substances that were not toxic and that could be phagocytosed by the cells of the body capable of doing so. The former approach led to the conclusion that the macrophages which invade inflamed areas and remove debris are comprised of both rounded histiocytes and transformed cells that enter from the blood. While this finding indicates that histiocytes round and change into forms which become morphologically and physiologically indistinguishable from the macrophages which represent activated blood monocytes, it does not answer the question of the ultimate fate of the macrophages from these two sources, nor of the origin of the histiocytes or their relationship to the free mononuclear phagocytes of the organs. It simply indicates that macrophages may arise by transformations of histiocytes and by transformations of monocytes, and that differentiation as to source ultimately becomes impossible by the techniques employed.

The attempts to determine the relationship of the phagocytic mononuclear cells in inflammation to those of the blood and tissues by use of vital stains resulted in other prolonged and confusing polemics. Vital stains are colloids, and their attraction to the phagocytic cells of the organism is due to their colloidal characteristics. The cells of the R-E system exhibit an elective attraction toward electronegative colloids. Schulemann[50] found that the most successful vital stains are the so-called diazo, benzidene, or acid dyes. Try-

pan blue is the most commonly used representative. Other particulate substances, however, such as india ink and carmine or colloidal iron, have served for many studies of the R-E system. The size of the particles of the colloid determine its diffusibility beyond the site of administration. When given intravenously the same factor determines if cells beyond the capillary endothelium are to receive the dye. Herein lay much of the cause for the confusion that arose as a result of attempts to determine the origins and relationships of the different R-E cells by the use of colloidal dyes. Those working with large-sized colloids given intravenously obtained staining of sinusoidal endothelial cells and such cells as arose from them, i.e., Kupffer cells and any macrophages which might have arisen from stained endothelial cells and wandered into the neighboring spaces. On the other hand, the pre-formed phagocytes away from the site of injection, the reticular cells, the histiocytes, and monocytes off in the tissues and away from the vessels did not stain for lack of access to the colloid. The histiocytes did stain, however, when the colloids were injected into the connective tissues directly. The concept of the endothelial origin of histiocytes and macrophages, the so-called "endothelial leucocytes," naturally arose from these studies; and reticular cells and monocytes were considered of separate line. With intravenous injections of dyes of smaller particulate size, however, which could pass through the capillaries, it was found that the histiocytes and macrophages then stained avidly without need for direct injection into the connective tissues, and that under those circumstances the reticular cells also stained. Furthermore, transitions were observed between the reticular cells and macrophages, as well as between the endothelial cells and macrophages. The monocytes did not stain and were believed to be a separate strain. The unlikelihood of this has been discussed previously. From these studies, then, there arose two ardent controversies, i.e., the origin of histiocytes and/or macrophages from endothelial cells only, or from reticular cells also. The relationship of the macrophages in areas of inflammation to monocytes from the blood stream and to rounded histiocytes has been discussed. The source of the histiocytes, whether simply resting wandering cells, i.e., macrophages, as believed by Maximow, or cells of separate origin, has not been definitively answered. The basic controversy, however, concerning the two fixed sources of origin of all the free mononuclear phagocytes of the body, i.e., reticular cells and sinusoidal endothelium, seems to rest upon the form of colloid used to trace the lineage. It was in recognition of this fact that Aschoff[1] and Aschoff and Kiyono[8] called the entire system, free cells and the fixed sources of origin, "the reticulo-endothelial system." The term has gradually become accepted, even by ardent believers of one or other origin, and the fact that some of the basic answers have not been settled is often unrecognized.

In the course of these studies with vital dyes, other as yet unanswered polemics arose. The studies revealed that sinusoidal endothelium is phagocytic while that of the capillaries in general is not. Therefore, Evans[18] called the sinusoidal linings "specific endothelium." It was also observed that the reticular cells of the organs which contain the specific endothelium also stain vitally, and in much the same manner. The obvious questions arose concerning the relationship of specific endothelium to ordinary endothelium and to reticular cells. Are the sinusoids lined by reticular cells rather than by endothelial cells; or are reticular cells and endothelial cells the same; or is specific endothelium just a more primitive form of ordinary endothelium; or does the endothelium stain in the sinusoidal areas simply by virtue of slowing of the blood in those areas and longer contact of the cells with the dyes?

The second polemic from these studies concerned itself with the relationship of the fibroblast of connective tissues to reticular cells, clasmatocytes, and the other phagocytic cells. When the colloidal particles for intravenous injection were large the fibroblasts stained no more than did the reticular cells and the histiocytes. When the colloidal particles were smaller, on the other hand, the fibroblasts stained. The staining was faint, to be sure, in contrast to that of the reticular cells and histiocytes, but the question of their relationship to the latter types naturally arose. Von Möllendorf,[35] in particular, is an ardent proponent of the concept that fibroblasts give rise to R-E cells. This concept has been refuted as a normal mechanism by most of the workers in the field, however, and is not seriously considered at present. The fibroblast is generally regarded as a mature cell which may be encouraged to phagocytosis under duress, and which then retains the dye for long periods, but which is not involved in the origin of R-E cells and does not exhibit the active metabolic capacities evinced by those cells.

The studies discussed thus far justify the conclusions that the free macrophages of the tissues may arise from reticular cells, specific endothelium, rounded histiocytes, and monocytes; that the relationship between reticular cells and specific endothelium is moot; that the origin of histio-

cytes is moot; and that the fate of the macrophages when their period of activity is over is moot, i.e., whether or not they revert to the less active stages of the R-E system.

While these studies and the arguments centering about the tissue macrophages were in progress a different polemic developed concerning the origin and fate of the monocyte. From their investigations concerning the origin of the different cells of the blood, Sabin and her collaborators[11, 45] came to the conclusion that monocytes arise from reticular cells and represent a separate strain of phagocytic cells from macrophages. As has been discussed, the weight of evidence is against this view today. Origin of macrophages from monocytes as well as from reticular and endothelial cells is accepted. This view, however, concerns merely the fate and not the origin of monocytes, and the question of origin remains. Those workers who were primarily interested in the origin of the cells of the blood, and who traced the transformations in those cells in the hematopoietic tissues and in areas of inflammation by means of stained fixed preparations, came to the conclusion that a single basophilic cell, called by various names but actually a young form of the lymphocytic series, gives rise to monocytes as well as to other cells of the blood. They, therefore, traced the origin of macrophages back to lymphocytes through monocytes.[8, 16] This point has never been answered satisfactorily. Yet it is one of the most important in the field of hematology, including the R-E system. The question of whether the lymphocyte is a multipotential or definitive cell is vital to an understanding of the diseases of the blood and to an understanding of the immune reactions of the body. Recent work indicates that lymphocytes may take an active share in the release of antibodies into the body fluids, under the stimulus of the adrenal cortex.[25, 61] Lymphocytes shed their cytoplasm under the stimulus of this hormone and must be rebuilt.[15] If they must function in the dual capacity of release of antibodies by their disruption and of conversion into phagocytes for defense, it would seem that the situation must occur when the former activity interferes with the latter. Whatever may be the final answer concerning the lymphocyte in these two respects, it seems probable that, despite its absence of phagocytic capacities, the cell must ultimately be included with those of the R-E system on one or the other score.

In recapitulation, then the controversial points centering about the origin and interrelationships of the various cells of the R-E system fall into the following main categories: (1) the relationship of lymphocytes to monocytes and, therefore, to macrophages; (2) the origin of monocytes, i.e., from lymphocytes or from reticular cells; (3) the origin of histiocytes; and (4) the relationship of reticular cells and specific endothelium to each other, and therefore, indirectly, to monocytes and macrophages. These are controversies of far greater than academic importance. Their answer will extend understanding of many of the problems concerning the physiology, function, and pathology of the system. One must be cognizant of the points of controversy concerning the immature levels of the system, in order to evaluate aberrant forms or aberrant activities within the system. Recognition of the controversial points concerning the interrelationships of the various cells of the system is necessary for any rational effort at stimulation or suppression of individual members of the system that in any way become out of balance with the other members of the system or that fail to carry out their particular activities. It is necessary to distinguish the proven from the controversial points concerning the interrelationships of the different cells of the system if one is properly to weigh the recurrent arguments concerning the relationships between different pathologic cells in the blood, between different hematologic states, and between malignant involvements of the R-E system and those of the blood and nodes. It is necessary to balance the proven against the controversial points, in order to evaluate the clinical syndromes in which the system is involved, syndromes involving hyperactivities of the system, infestation of one or other cells of the system, abnormal metabolism or perverted functions within the system. Awareness of the controversial points not only permits of adequate evaluations, but, what is of equal importance, it favors recognition of support or refutation to controversies, should they be accidentally met in the course of clinical or experimental studies undertaken for different purposes.

Phagocytosis Within the R-E System

While all the cells of the R-E system are more or less phagocytic, there is considerable difference in their capacity as judged by the size and variety of the particulate matter which the different members of the system can handle. The fixed reticular cells and the free monocytes represent the least phagocytic forms normally. Ordinarily they phagocytose sparingly and small-sized particles only. They may become extremely active under stimulus, as has been discussed, and in that case they soon become morphologically and

physiologically indistinguishable from macrophages (Plate 1). Metchnikoff[34] believed that macrophages engulf chiefly materials of animal origin or nature, such as erythrocytes, malarial parasites, etc., or organisms that cause chronic infections, while those that cause acute infections are taken by the macrophages. Actually the engulfment of parasites and other cells of animal origin is apparently associated with the fact that the cells of the R-E system may phagocytose large as well as small particles, and animal cells are relatively large. Macrophages may, however, engulf bacteria and many other particulate bodies, such as lipids and colloids of various nature, as well as whole or fragmented animal cells. As has been stated, they exhibit a predilection for electronegative colloids of a wide variety. They clear the tissues of particles of carbon whether administered parenterally or inspired. The phagocytes of the lungs and bronchial nodes contain quantities of carbon. R-E cells phagocytose iron filings and various metallic particles, such as gold, radioactive metals, manganese, dust, silicon, etc. They have been demonstrated to phagocytose large protein particles, such as agar, in the same manner. The latent harm to the organism from therapeutic or industrial administration of such substances is associated with the response of the R-E cells to substances which they find themselves unable to destroy and therefore release over and again to the organism. They respond normally and avidly to effete or foreign red cells (Plate 4), to phospholipids[55] (Plates 2 and 3, Fig. 1-9) and to cholesterol[57] in colloidal form. All of these examples represent phagocytosis of particles that are demonstrable within the cells by their microscopic characteristics. Phagocytosis of particles that cannot be optically distinguished within the cytoplasm of the cells is more difficult of demonstration but seems quite likely. The possibility of the phagocytosis of large protein molecules of biologic significance, either normally or to abnormal degree, and the importance of this to the functions performed by those proteins is fascinating.

The attraction of the cells of the R-E system for colloidal particles has been employed on many occasions for the production of so-called "blockade" in experimental efforts to modify the action of the system toward bacteria or other colloids, or to decrease the activity of the system when such activity is believed to be undesirable, as in allergic responses. The possibility of blocking the system is moot (see Jaffé, p. 1042). If blockade is possible, it should be subject to activation spontaneously as well as therapeutically and result in hypoactivity of the system. Yet spontaneous blockade has not been observed. The capacity of the system for hypertrophy and hyperplasia is so

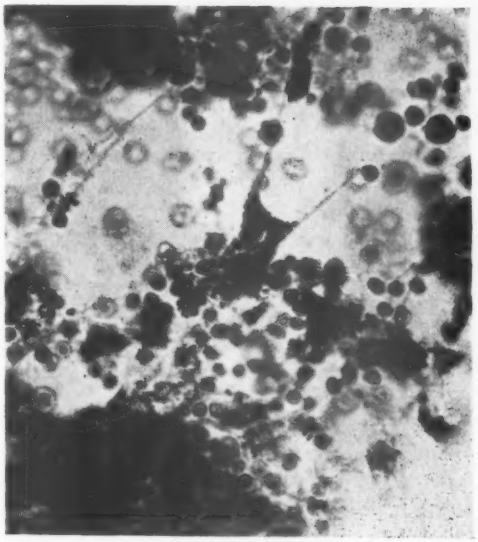


Plate 1—Lymph node of a rabbit. Reticular cells and macrophages have hypertrophied and become almost indistinguishable by virtue of experimental ingestion of the phosphatide, lecithin. Stained with nile blue sulfate.

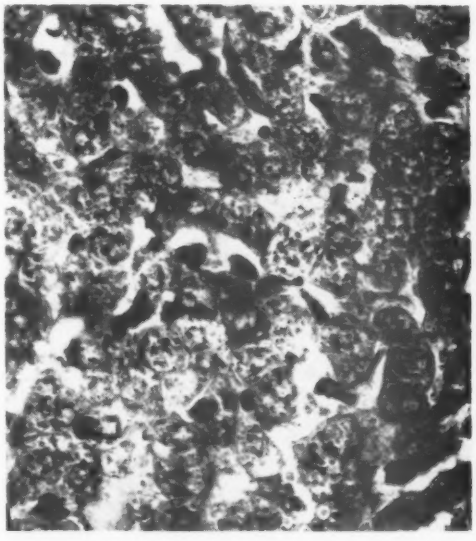


Plate 2—Liver from same rabbit as plate 1. The Kupffer cells are laden with ingested lipids. Stained with sudan 4.

pronounced that prolonged blockade seems unlikely. The studies with vital dyes have demonstrated the remarkable ability of the system to expand to the demands upon it and rapidly to produce new and larger cells to meet them. Further, these studies have demonstrated the capacity of the cells to phagocytose new colloids when already loaded with others. One and the same cell may phagocytose red cells, debris, diazo dyes, and particles like carbon and carmine at the same time. It seems that blockade would be most likely to function, if at all, only when produced just ahead of introduction of the substance whose phagocytosis is to be inhibited, i.e., only when the substance to be inhibited is introduced immediately after all of the exposed cells of the system have been subjected to the blocking materials and before new free cells can be liberated. Even at that, blockade by mere virtue of filling the cells with other non-specific colloids seems unlikely. It would seem as if the materials used for blocking must be of such nature as to detract substances which would otherwise be attracted if blockade is to be even temporarily successful. Since the cells have a predilection for electronegative colloids and the activity of colloids is modified by pH and electrolytes, modification of the charge of R-E cells by their phagocytosed particles or by shifts in their pH or electrolytes might result in temporary detraction or blocking; or, the size of the particles to be phagocytosed might be modified by similar forces. These are approaches which need investigation. The studies of Seki[51] are pertinent to these concepts.

The mechanism of phagocytosis received considerable study in the past. The subject was reviewed by Mudd, McCutcheon, and Lucké[36] in 1934, and is further discussed by Jaffé.[26] The interest in such studies has subsided. The outcome of these studies leads to the conclusion that phagocytosis represents a combination of several forces. The free cells of the R-E system are motile and contain delicate waving ectoplasm which is capable of enveloping particles which may later be withdrawn into the more central areas of the cell as the latter withdraws its outlying film of ectoplasm. This represents, in part at least, an active process. On the other hand, other types of cells with even greater powers of motility, and with far more active pseudopodal activity, often do not attract substances which are actively engulfed by R-E cells. In contrast to the failure of the granular leucocytes, for instance, to attract electronegative colloids, erythrocytes, and colloidal cholesterol, R-E cells exhibit characteristic attraction of these particles. In the case of the latter cells, therefore, the capacity for phagocytosis represents a combination of at least two forces, i.e., colloidal attraction and active inclusion of such particles as are attracted. A further force, at times at least, seems to involve the enzymatic capacities of the cells. In the case of colloidal cholesterol, for instance, the tiny crystals which are electively attracted to the surface of the macrophages and histiocytes appear to be converted into esters at the cellular surfaces and to be taken into the cells as such.[57] At other times phagocytosis seems to involve a preliminary solution, or suspension, of particles which the cells will not phagocytose otherwise, into more easily assimilable materials. Hydrophobic particles of galactolipids, for instance, have been shown to be taken into macrophages in conjunction with easily phagocytosed phospholipids, while the macrophages are not activated toward the former alone.[54] Phagocytosis, then, seems to represent one or more of several activities, i.e., colloidal attraction, active ingestion, enzymatic or chemical changes at the cellular surfaces, and mixed solubilities. Passage of materials into cells by diffusion is disregarded here as a means of phagocytosis, even should the materials later be precipitated within the cells and appear as particulate matter. The term phagocytosis is limited to include the absorption of matter that is particulate on the outside, before it enters the cell.

Since phagocytosis represents a combination of several forces, it may obviously be modified by changes in those forces. The degree by which any given substance is phagocytosed may not only be modified by changes in the capacities of the R-E cells to attract, to ingest, or to convert substances at their surfaces into more assimilable form, but may be changed by modification of the particles to be phagocytosed, i.e., by changes in the charge and size of the colloidal substances themselves outside the cells. It is because of the variety of possibilities, and the relatively little that is understood about them, that discussion always arises in cases of hyperactivity of the R-E system as to whether increased phagocytosis is due to changes within the system itself or in the substances being phagocytosed.

The answer to the relative significance in the act of phagocytosis between attraction on the part of the R-E cells and the factors within any particles that are so attracted must remain problematic until more is understood concerning the forces in R-E cells that cause them to attract, and

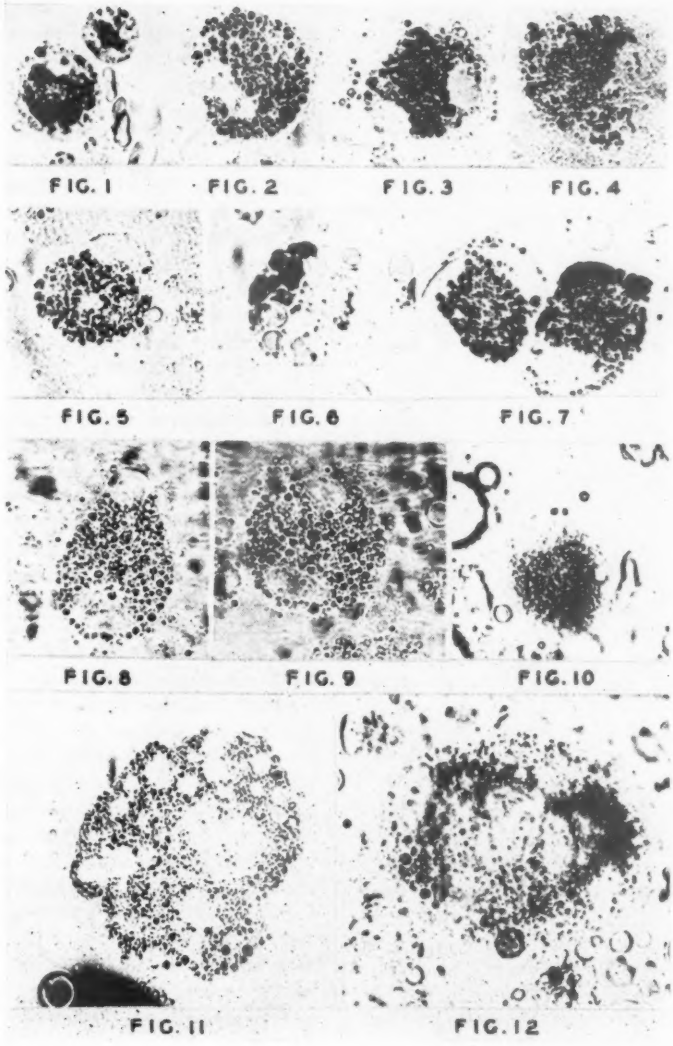


Plate 3—Taken from "The Reaction of the Connective Tissues to Lipides and Other Foreign Bodies" by Edna H. Tompkins (53).

Supravitally stained macrophages from guinea pigs following subcutaneous injections of lipids or mineral oil. The areas that stained supravitally with neutral red appear black in the photograph.

Fig. 1-4—Macrophages that had ingested egg lecithin.

Fig. 5-7—Macrophages that had ingested the ether insoluble fraction of brain lipids.

Fig. 8-9—A single macrophage before and after ingestion of a mass of egg lecithin.

Fig. 10-12—Epithelioid cell and epithelioid giant cell, respectively, from an area injected with mineral oil.

the ways in which those forces are modified by changes in the electrolytes and pH of the cytologic contents and by previous phagocytosis of substances that might modify the overall charge of the cells, and until such knowlege is correlated with the effects of similar factors upon the colloidal substances to be attracted from the mediums outside the cells.

Metabolic Activities of the R-E System

The manner in which R-E cells respond to the various substances which enter their cytoplasm by phagocytosis depends upon the chemistry of the substances and upon the metabolic capacities of the different members of the system. Use of appropriate metabolites offers an alluring method for determination of the presence or absence in R-E cells of enzymes needed in the intermediary metabolism of various foods, and, vice versa, for analysis of the manner by which R-E cells digest various substances and synthesize others to be returned to the body fluids. The possibilities inherent in this approach have been utilized very little except from broad aspects. Metchnikoff[34] found that macrophages not only phagocytose particles of animal origin, such as erythrocytes, spermatozoa, and other cells, but that they digest these in some manner and apparently excrete the products. He therefore recognized that they contain proteolytic enzymes and was able to establish that these act only within the cells. He considered them analogous to trypsins and found them effective in neutral and weakly acid or alkaline environments. Opie[38] states that the proteolytic enzymes of macrophages in areas of inflammation react only in acid medium and are therefore pepsin-like. Firket[20] obtained similar results with the extract of crushed tissue cultures which contained a large component of histiocytes.

R-E cells are accepted as the sole site for removal of effete erythrocytes and for the initial analysis of these into simplified products which may be eliminated by the body or further utilized. Yet the stages in these processes are but poorly understood. All workers in the field have seen the free cells of the system loaded with erythrocytes in various stages of disintegration leading to a residuum of iron split from its organic combination in hemoglobin to a substance, hemosiderin, which gives the prussian blue reaction of inorganic iron. Rich[43] was able to demonstrate both the production of inorganic iron and the liberation of bile pigments by these cells in vitro, thus corroborating their activity in the intermediary stages of pyrrole metabolism as well as in the life cycle of the red blood cells. The enzymes involved may be surmised but have not been demonstrated. Nor has the final fate of the iron-containing portion of the hemoglobin molecule within the cells been determined, nor the chemical form in which the iron of the molecule is ultimately returned to the circulation for re-elaboration into hemoglobin within new erythrocytes (Plate 4).

In similar manner it has long been recognized that the cells frequently contain droplets of lipid, but little attempt has been made to determine the source, type, or fate of the same. Ralph[40] has shown that monocytes contain phospholipids and acetone-soluble fats. It has been assumed by many that when found these droplets have resulted from the breakdown of previously phagocytosed cells. It is also known that the cells phagocytose lipid particles if met free in the tissue spaces. The fate of such lipid is inadequately determined. That the cells may share in the normal metabolism of ingested fats has been suggested but not demonstrated. Tompkins[55] has shown that macrophages are capable of copious ingestion and complete digestion of the various groups of phospholipids (Plate 3, Fig. 1-9) but has not demonstrated the intermediate stages or enzymes involved. She has shown that they are also able to convert cholesterol into esters, and that they therefore apparently contain cholesterol esterase.[57] The esters eventually disappear from the cells with concomitant changes in the phagocytic vacuoles that stain with neutral red, and the hypothesis is suggested that the esters become bound as lipoproteins and are excreted back into the tissue fluids in that form. This concept, however, is in need of extended study.

Gray[24] has shown that macrophages phagocytose neutral fats but are injured thereby, except in the case of tributerin. Sabin, et al.[46] have shown the same for the waxy coat of tubercle bacilli and have demonstrated that the injurious effects are due to the component of phthioic acid in the tuberculo-phosphatide. Various fatty acids were shown to cause similar injury to macrophages together with intense irritative reactions on the part of the tissues in general. The assumption may be drawn, therefore, from these reactions to neutral fats and to tuberculo-phthioic acid, that macrophages either contain lipases that split off free fatty acids which then harm the cells, or that they are incapable of further metabolizing these substances and that the latter harm them as foreign bodies. Injury of R-E cells by many foreign bodies which they cannot digest is an accepted fact.[46, 53]

The presence of lipases was assumed by Metchnikoff[34] on the basis of various observations, and has long been believed to be supported by the in vitro studies of Bergel.[5] Bergel called the cells with which he made his studies lymphocytes, but, as Aschoff and Kamiya[2] concluded, he must actually have employed the macrophages of inflammation. Recent histochemical studies by Gomori,[22] on the other hand, failed to reveal lipase in areas so rich in R-E cells as the spleen and lymph

nodes, although it was demonstrated in the interstitial cells of the pulmonary alveoli, cells that belong to the R-E system. It is possible that the technique employed is limited to more specific lipases than is realized. In any case, the need for further elucidation of the role of R-E cells in fat metabolism is obvious, and the possibilities inherent in the use of specific lipides and appropriate cytochemical techniques are evident.

New cytochemical techniques have developed rapidly in recent years. They may be divided into those which employ improved or modified optics, such as phase, electron, polaroid, dark field, and ultraviolet microscopy, and those which represent cytochemical techniques. The former permit better definition and detection of particulate bodies, but only limited analysis of the composition of the bodies. The latter make use of selective digestion, solution, staining, diffraction, etc., of specific substances within tissues and cells and permit of differential analysis in so far as the techniques in question are definitive. The R-E system has received little direct study by these techniques, and deductions concerning the reactions of the system to them must be culled from studies of organs that contain R-E cells.

Supravital and vital studies have been employed to demonstrate not only the normal phagocytic and metabolic capacities of the system, as has been discussed at length, but to reveal abnormalities of metabolism which will be discussed later. These studies to date, however, have been limited mostly to determinations of a quantitative rather than a qualitative nature. Discussion has been presented elsewhere in this journal[59] of the possibilities inherent in analysis of the transformations that occur during digestion within the so-called phagocytic vacuoles that stain with neutral red. Koehring[31] has contributed a valuable study of the physical characteristics of these vacuoles.

The supravital technique permits detection and differential staining of mitochondria in the unfixed state, and has demonstrated that the free cells of the R-E system contain many rod-shaped mitochondria which are finer than those in lymphocytes and are scattered throughout the cytoplasm. These organoids have been studied from other types of cells by various techniques and have been shown to represent combinations of phospholipids with proteins which are enzymatic in character and concerned with the aerobic energy requirements of the cells. They have been found to be associated with succinoxidase activity and cytochrome c, by Schneider, Claude, and Hogeboom,[48] and with the fatty acid oxidase system by Kennedy and Lehninger.[28] Studies concerning

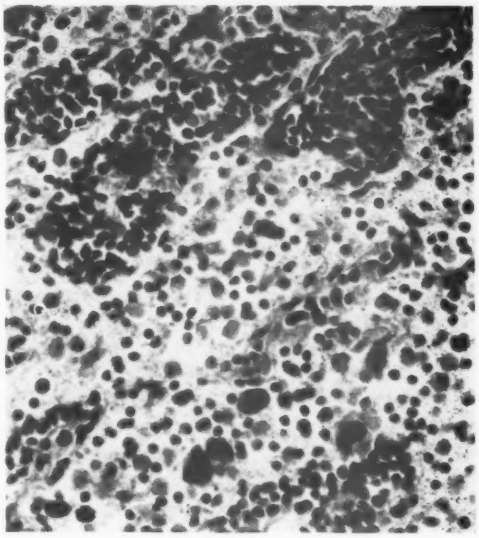


Plate 4—**Lymph Node from same rabbit as plates 1 and 2. The macrophages contained hemoglobin in various stages of disintegration. Digestion with trypsin followed by staining with the Prussian blue reaction.**

these enzymes in the R-E system have not been reported, but the presence of oxidases and peroxidases in general, without regard to specificity, has long been acknowleged for the free cells of the system, i.e., monocytes, histiocytes, and macrophages. With the histochemical tests employed, these occur as discrete granules scattered diffusely throughout the cytoplasm. It seems quite likely that they include those enzymes which have been found to be associated with mitochondria elsewhere. Corroboration of this is, of course, indicated. And detailed analysis concerning the life cycle of mitochondria in the various stages of the R-E system is needed.

Application of Gomori's techniques for acid and alkaline phosphatases in the study of various organs which are rich in R-E cells has resulted in contradictory reports concerning those cells. The exact significance of these phosphatases has not been established. They are probably concerned with both the analysis and synthesis of the intermediary compounds in the metabolism of proteins, nucleic acid, glucose, and phospholipids. Dempsey and Wislocki[13] discuss their relationships to other cytologic components. Kabat and Furth[27] state that alkaline phosphatase is present wherever active absorption and elimination of glucose occur. Deane[12] has demonstrated the activity of alkaline phosphatases toward a variety of organic combinations with phosphoric

acid other than those of the intermediary metabolites of glucose. The significance of acid phosphatases in contradistinction to alkaline phosphatases is not known.

Gomori[22] did not mention R-E cells specifically, but the sparsity of reaction for alkaline phosphatases in such organs as the spleen and nodes would lead to the assumption that the R-E cells within them do not contain alkaline phosphatases. The findings of Kabat and Furth[27] and of Bourne[10] support the same conclusion. Emmel,[17] on the other hand, observed a positive reaction for alkaline phosphatases in the R-E cells of the spleen, and Deane[12] obtained a positive reaction in Kupffer cells with a variety of substrates. Her only negative finding was for lecithin phosphatase. Positive findings with these techniques are more significant than negative ones; and the diversity of organic substances which these cells are known to digest would also strongly support the supposition of the presence of alkaline phosphatases in their cytoplasm. The reports concerning the acid phosphatases in R-E cells are in agreement. Gomori,[21] Deane,[12] and Wolfe, Kabat, and Newman[62] found acid phosphatases in the R-E cells of the spleen or liver. Direct examination of R-E cells with appropriate substrates for different phosphatases at the different stages of growth and phagocytic activity of the cells is obviously needed for better understanding of their capacities toward the intermediary metabolites.

The apparent capacity of the cells of the system for complete digestion of many organic materials, and their component of phosphatases would lead to the belief that they exercise considerable synthetic ability. This belief is strongly supported by the characteristic basophilia of the cytoplasm of all the cells of the system. Basophilia may be due to several cytologic components, one of which is ribonucleo-protein. The nucleoproteins have been discussed by Dempsey and Wislocki.[13] Ribonucleo-protein, in particular, is credited with activity in the synthesis of proteins. Its presence in any given cell is accepted as evidence of the elaboration of proteins by that cell. Rheingold and Wislocki[42] demonstrated its presence in the cytoplasm of all of the cells of the bone marrow. This may be supposed to include the R-E cells scattered among the crowded blood cells, but corroboration by direct determination with one of the methods now available is needed. The nuclei of these cells contain moderate amounts of desoxyribonucleo-protein. Those of some of the series contain very large nucleoli which have been found to consist mainly of ribonucleo-protein. Correlation of the variations in amount of these nucleo-proteins at different stages in the growth, metamorphosis, and metabolic activity of the different cells of the system should help considerably in clarification of some of the controversies concerning the interrelationships of the cells and the pathologic activities and anomalies of the same.

Schudy[49] found an actively fluctuating component of vitamin C in various cells of the R-E system. Increments were related to stimulation of the adrenals, with depletion of vitamin C in the latter. Savers, Sayers, Liang, and Long[47] obtained similar depletion of the adrenals together with loss of cholesterol following administration of pituitary adrenotrophic hormone. The significance of the reciprocal relationship in content of vitamin C in adrenal and R-E cells is not yet understood but is related to the response of the R-E system in shock and immune reactions. This will be discussed later. Popper[39] has demonstrated vitamin A in the Kupffer cells of the liver.

This brief survey of the available information concerning the enzymatic activities of the system serves to indicate how little specific study has been done on the subject and how much the accepted activities of the cells rest upon assumption only. One might possibly assume that they obtain certain of the enzymes needed for their protean activities simply by virtue of their power to phagocytose the same from other tissues. The effectiveness of enzymes obtained in this way, and therefore subjected to foreign intracellular forces, however, is open to question.

The need for careful investigation of the metabolic capacities of the different cells of the system with even the limited techniques now available is great. Determination of their metabolic capacities, not only as an overall picture, but for specific details related to the intermediate metabolism of proteins, fats, and carbohydrates would greatly aid in evaluations of the importance of the system in normal metabolism, in disease, and in defense mechanisms. If these studies could be correlated with the differences in phagocytic activity of the various members of the system, particularly of the free members, it seems likely that many of the controversies of the past based on morphologic differences with single or uncorrelated techniques could be simultaneously settled.

Relationship of the R-E System to Defense Mechanisms of the Body

Thus far the discussion has concerned the interrelationships of the cells of the R-E system and

the known facts concerning their normal phagocytic and metabolic activities. The system has long been credited, however, with defense mechanisms other than those of phagocytosis and destruction of the phagocytosed substances. It has been credited with elaboration of various antibodies, such as antitoxins, agglutinins, hemolysins, etc. An association of the system with these activities was indicated by Metchnikoff's[34] studies, and many clinical and experimental observations since his time have supported his concepts. It has come to be accepted that the system takes a dominant part in such reactions, and probably elaborates the antibodies to the substances which it has phagocytosed and changed within its cells. Incontestable evidence of this has not been obtained, however. The blood-forming organs, including the bone marrow, spleen, and nodes, become hyperplastic and hypertrophied in infections and other states that call forth immune reactions. They are involved in allergic responses. These organs contain a variety of cells including different members of the R-E system. The latter multiply, swell, and enlarge in infection or during passive sensitization. Definitive experiments indicative of the presence of immune substances within them, or within any of the other cells of these organs, have not been forthcoming, however. It has long been recognized that fragmentation of the cytoplasm of the more active members of the R-E system may occur; hence the name of clasmatocytes given to them by Ranvier.[41] But the cause and significance of this fragmentation are not certain. The findings of Sabin,[44] following injections of a foreign protein linked with a dye, indicate the probability that fragmentation is a mechanism by which the cells liberate cytoplasmic constituents which are in some way related to the production of immunity. Sabin followed the response of the R-E cells and the titer of antibody to the protein of the dye in the serum subsequent to the injections and found that the macrophages which had phagocytosed the dye-protein lost fragments of their cytoplasm at about the same period that antibodies began to appear. The presumption is evident that the cells elaborated the antibodies in response to the presence of the dye-protein within them and then freed them to the body fluids by the method of cytoplasmic fragmentation. The changes in the vacuolar apparatus of the R-E cells following ingestion of many substances to which the organism produces antibodies, including such easily observable particles as foreign red cells, suggest that the contents of the vacuoles may represent not only breakdown products of the phagocytosed substances but elaborations on the part of the cells of new proteins from those products. Baker[4] has demonstrated that the Golgi apparatus of other cells is composed of arrangements of lipo-protein that include vacuoles which stain with neutral red, and which lie within the synthetic area of the cells. In R-E cells many vacuoles stainable with neutral red are always found in the region allocated to the Golgi apparatus as well as scattered in the cytoplasm.

Evidence has accumulated, then, from both clinical and experimental findings, to associate R-E cells with the elaboration of proteins from the products of ingestion which may or may not be antibodies but which are related to antibody formation. Correlation of the data from various approaches would seem to link the metabolic vacuoles and the area of the Golgi apparatus with this production. Excretion of these products may be by cytoplasmic shedding, as found by Sabin,[44] or by diffusion if the products are diffusible. At any rate, even though definitive proof is lacking, the accumulation of evidence, from the time of Metchnikoff's fascinating observations of the reactions of macrophages to initial and repeated injections of foreign red cells, has associated the cells of the R-E system with the production of antibodies.

Two groups of recent studies concerned with immunity have complicated the story considerably. These consist of: (1) the studies from the Scandinavian school, Bing and Plum,[6] Bjorneboe and Gormsen,[7] etc., which implicate plasma cells as the source of antibodies and demonstrate widespread production of these cells in the course of immunization; and (2) the studies by several groups of American workers, Dougherty, et al.,[14] White and Dougherty,[60], Harris and Ehrich,[25] and Simpson, et al.,[52] which implicate the lymphocyte as the source of antibodies. These latter workers have shown that the cytoplasm of lymphocytes is shed under the influence of hormones from the adrenal cortex. Gamma globulin and a high titer of pre-existing antibodies enter the blood as the lymphocytes disintegrate. They conclude that these substances arise from the cytoplasm of the lymphocytes. The explanation for the presence of antibodies in lymphocytes, which are not phagocytic cells, is questionable. Harris and Ehrich[25] present experimental data in support of the concept that R-E cells merely convert particulate antigens which they phagocytose into soluble antigens and that the latter are then carried to the lymph nodes with subsequent

elaboration of the antibodies by lymphocytes. Explanation has not yet been offered for the ability of the adrenal cortical hormone to cause disintegration of the lymphocytes and liberation of antibodies. The effect of sphingomyelins, one group of phospholipids, upon blood cells should be mentioned in this connection. Tompkins[58] found that intravenous injections of sphingomyelins produce the same effects on circulating lymphocytes as are produced by the pituitary adrenotrophic hormone, and that the circulating monocytes respond in parallel manner (Chart 1). The explanation for this effect from sphingomyelins is not known. Lymph nodes contain an abundance of monocytes and these increase markedly under stimulus. It seems probable from these findings that the antibodies liberated into the blood stream in the preceding experiments could be derived from either cell, and that the conclusion that they are derived from the fragmented lymphocytes is still open to question. The polemic concerning the relationship of lymphocytes to monocytes, which was discussed previously, is obviously of significance here.

The implication of plasma cells in the production of antibodies by the workers in the Scandinavian school needs correlation with similar studies by other cytologic techniques before it can be properly evaluated. There is no argument as to the hyperproduction of the cells in question in states of hyperimmunization, but the identity of the cells needs clarification. The identity of "plasma cells," their origin, function, and fate, have always been problematic.[9] The relationship of the cells stimulated by these workers to lymphocytes, on the one hand, and to monocytes and macrophages, on the other hand, and their response to adrenal cortical stimulus should be investigated. The possibility should also be considered that they are incidental to other factors at play during the processes of immunization and are not necessarily the locus of antibody formation.

As the matter stands at present the relationship of R-E cells to immune reactions is uncontested. But in what way and how far they function in this connection have become controversial. The implication of other cells in the production and storage of antibodies, as well as in their release, now needs to be considered.

The R-E System in Pathologic Processes *

As in the case of the other organs of the body, it is conceivable that the R-E system may become hypo- or hyper-active in one or other or all of its functions and give rise to characteristic disease of the organism as a whole. Or the activities of the system may become perverted at certain cytologic levels with resultant abnormalities within its own cells, as well as within the organism as a whole. Or the system may perform its action of phagocytosis normally but be unable to destroy the type of material which it has ingested and itself become injured in the process. These and other possibilities must be considered in each instance of abnormal activity or dysfunction on the part of the system.

Incapacity to destroy completely the object of phagocytosis is accepted as partial explanation of the spread and chronicity of tuberculosis and leprosy, of kala azar, of histoplasmosis (Plate 5) and malaria. In each instance the R-E system destroys the organism involved with difficulty and is believed to act in part as harbor for it, and even as a culture medium. While the cells succeed in injuring certain of the organisms, enough survive to propogate within the cells with eventual injury and death of the invaded cells and their own liberation for continued spread. The free cells of the system which become injured in the process often become converted into pathologic forms of the system, epithelioid and giant cells, before they ultimately succumb. Epithelioid cells apparently cannot perform their functions of digestion and multiplication adequately and are characterized by an unusual fineness, evenness, and dark color of the vacuolar apparatus, by accumulation of sudanophilic fats and by amitotic division with frequent occurrence of two or more nuclei. The giant cells are of two types, of which one, the Langhans giant cell, has a vacuolar apparatus like that of epithelioid cells. Both contain many nuclei. These cells may also occur in response to phagocytosis by the monocytes and macrophages of many other foreign substances which they cannot adequately handle[46, 52] (Plate 3, Fig. 10 and 12).

Abnormal response on the part of the system is evoked as one of the possible explanations for the so-called lipoid storage diseases, i.e., Niemann-Pick disease, Gaucher's disease, Schüller Christian's disease, and xanthomatosis. In these conditions the cells of the system are increased in number and tremendously hypertrophied and filled with large deposits of the lipid characteristic of the particular disease in question. Argument as to the etiology of these conditions sways between two possibilities: (1) incapacity of the R-E system to digest the lipid in question as it is brought to it in the normal course of events, and (2) over-supply of the lipid in question due to failure

* See Jaffe[26] for detailed discussion.

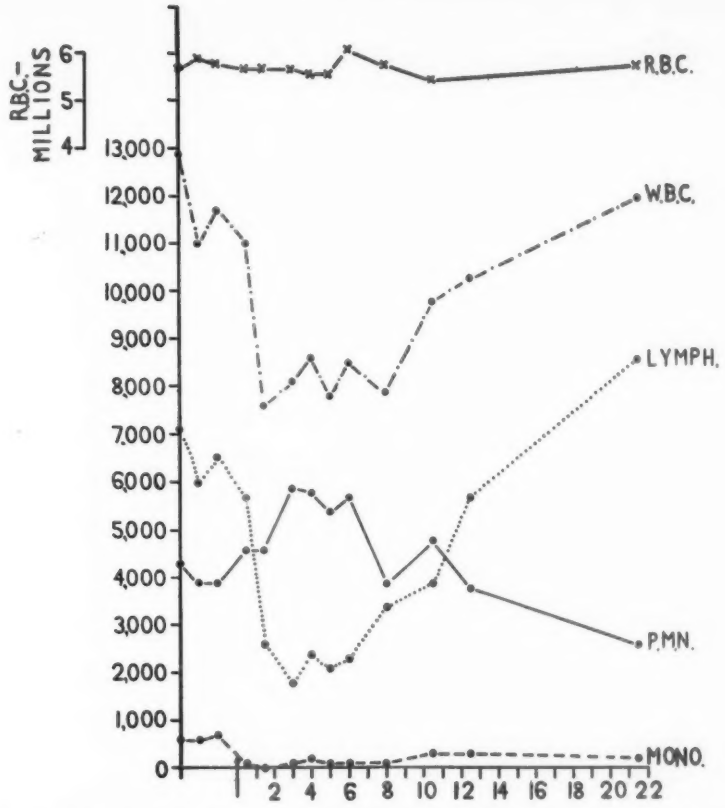


Chart 1—**Taken from "Sphingomyelins: Their Action on Blood Cells, Particularly Lymphocytes: Their share in the Nucleinate-Like Action of the Ether-Insoluble Fraction of Brain Lipids" by Edna H. Tompkins (58) (Chart 3.)**

Absolute numbers of circulating blood cells. An intravenous injection of a rabbit with sphingomyelins was made at the point indicated by the arrow. The circulating blood cells responded as after injections of pituitary adrenotrophic hormone.

on the part of some other system of the body. On the whole, the cells of the R-E system do not show the evidences of degeneration in these conditions which one might expect were they loaded with particles which they cannot digest. They seem, rather, to contain substances in the process of digestion. Tompkins[55, 56, 57] produced similar cells in normal animals simply by excessive supply of the lipids in question, and the stored materials disappeared from the cells normally if the supply were discontinued and sufficient time for digestion were allowed. Ferraro and Jervis[19] obtained comparable results. It seems probable that the storage of lipids within the cells in these conditions simply represents response to excessive supply rather than to inability on the part of the cells to carry digestion to completion.

Similar argument arises in those states of hypersplenism characterized by excessive phagocytosis of red or white blood cells. The R-E system in these cases is hyperplastic and its cells are loaded with the particular blood cells in question. The condition could involve the R-E cells primarily and thereby lead to the abnormal ingestion of blood cells, or it could involve the blood cells primarily and result in their abnormal attraction toward the R-E cells, in which case the latter would merely have responded secondarily to the stimulus from without. Although the benefit derived from splenectomy in these cases is usually attributed to removal of a large reservoir of R-E cells and assumption of initial disease of the same, this is not necessarily correct. The spleen is an organ peculiarly adapted to the exposure of blood cells to trauma, as well as to phagocytosis, and abnormal conditions within its sinusoids, or of the cells

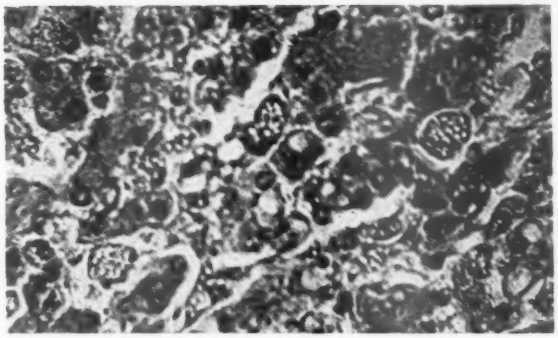
flowing through them, could result in considerable destruction of the latter and a resultant phagocytosis of the same without assumption of abnormality on the part of the R-E system (Plate 6). The erythrophagocytosis which Knisely[30] obtains under conditions of "sludging" is illustrative. Benefit from removal of the spleen, therefore, gives no direct indication of which process is ethiologic.

In the various hyperplastic states discussed thus far the system seems stimulated to essentially normal, though excessive, functions, irrespective of whether the stimulus is the result of a primary hyperactivity of the R-E system or of a secondary response to disease of some other system of the body. Primary disease of the system is much more evident in those conditions where one or other type of R-E cell multiplies at the expense of other members of the system and of the neighboring structures. Not only is there hyperplasia of some one cell of the system in these cases, but the cell itself often becomes pathologic in appearance and seems to fail in the performance of its normal activities. Conditions of this type may be grouped under two main headings, i.e. the tumors and the leukemias.

The involvements in the former group comprise localized multiplications of some certain cell of the system with a scattering of similar circumscribed masses by either metastasis or disseminated stimulus. The involvement in the latter group is diffuse and widespread throughout the blood-forming organs with invasion of other tissues directly from the blood and sites of origin of R-E cells. The tumors may be composed predominantly of reticular cells, endothelial cells, mixtures of these, or of the more phagocytic members of the system. They are called reticular-cell tumors, reticulo-endotheliomata, endotheliomata, reticular-cell sarcomas, Hodgkin's disease, etc. The leukemias may involve primarily monoblasts, monocytes, or clasmatocytes and are called monocytic or clasmatocytic leukemias, respectively. The questions concerning the etiology of the tumors and leukemias of the R-E system, their prognosis and their treatment, are those of malignancy in general and will not be discussed.

Since one of the accepted functions of the R-E system seems to be a share in the production of immune bodies to various allergens, states of hypersensitivity and of allergic manifestations are naturally often attributed to overactivity of the system. It is on the basis of such reasoning that efforts at blockade have been directed toward suppression of allergic responses. Discussion of blockade has been presented in the section dealing with phagocytosis in general. The validity of the assumption of a pathologic activity of the R-E system in hypersensitiveness and of treatment through attack upon the system must remain problematic until the question of the part played by lymphocytes and plasma cells in the formation and storage of immune bodies and of the action of the adrenal cortex in the liberation of these bodies can be better answered.

The fact that the R-E system is normally concerned with the phagocytosis and destruction of noxious particles lends hope to the possibility that ways will be discovered by which it may be therapeutically encouraged to increased activity, to the phagocytosis of substances to which it is ordinarily but mildly attracted, to an ability to destroy organisms that it does not normally handle successfully, and to ingestion and concentration of specific substances harmful to those specific organisms which it merely harbors without destruction. These possibilities lend purpose and interest to all studies concerned with the normal activities of the system. It is normally stimulated to multiplication and increased activity by parenteral injection of those colloids which have been found to be easily phagocytosed. Introduction of foreign erythrocytes, of injured homologous erythrocytes, of certain lipids, and of the colloidal dyes causes increase in the number of these cells and in their phagocytic activity. These substances in themselves may involve toxic reactions, however, and too little is understood about their fate within R-E cells for successful results from their use as yet. Invasion of the organism by certain pathogenic forms, such as Bacillus melitensis, acid fast bacteria, and certain fungi, stimulates increased production and phagocytosis on the part of R-E cells. The inability of the cells to cope with such invaders again operates against their use. R-E cells must be stimulated by other means before their responses can be helpful. The cells may be stimulated by injections of foreign proteins. This method is in use in the production of artificial immunization but until more is understood of the role of the system in immunity this method is obviously open to objection as a means of stimulation to non-specific combat. Hyperplasia of the system has resulted from therapeutic or experimental administration of various metallic or organic colloids which the cells are unable to digest and which ultimately injure them and cause fibrosis. The possibility of the use of some of these substances in lesser amounts to change the normal forces of attraction in R-E cells or to affect undestroyed organisms within the cells seems still open to investigation. The use of colloids which the cells can digest normally as



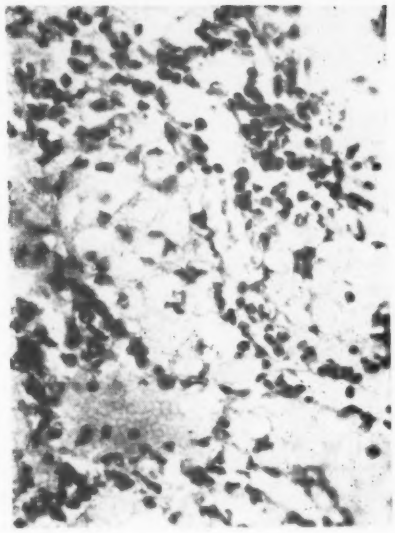


Plate 5 (above)—Liver. Human case of histoplasmosis. The sinusoids were crowded with macrophages which contained many parasites.

Plate 6 (right)—Spleen. Rabbit. Experimental production of Gaucher's disease by intravenous injections of the ether insoluble fraction of brain lipids. The sinusoids were constricted by the cords of swollen reticular cells so that blood cells passing through them were subjected to abnormal mechanical trauma in addition to exposure to an increased number of phagocytes.

carriers of other substances, as well as stimulants to multiplication, needs investigation.

Conclusion

As stated earlier, this discussion is in no way meant as a complete summary of the maze of contributions that have centered about the R-E system. It was planned as a means of correlating the known facts and chief controversial points in an effort to make clear where accepted concepts about the system are based on fact and where on assumption. The relationship between this system and the hematopoietic system, within the more strict confines of the latter, has been indicated. The work was undertaken in order to determine where more recent studies, especially of a cytochemical nature, have been used to explore the system and where such exploration has been inadequately performed with the newer techniques at hand. The attempt has been made to indicate where recent contributions concerning other systems of the body impinge upon questions that involve the R-E system, to point out where the normal functions of the system are understood and where in doubt, and to define the controversies centering about pathologic involvements of the system. Space has been taken for discussion of questions involved in efforts to stimulate the system, and of the directions in which stimulation of the system might be attempted on a rational basis. Finally, this has been written with the hope that awareness of the controversial points not only may safeguard against the erroneous deductions and procedures that may occur where distinction between fact and assumption is vague, but may encourage alertness to instances where findings in related lines of study may apply to points of controversy.

The system is ubiquitous; it is capable of tremendous hyperplasia; it is composed of fixed and of free cells. The latter are relatively complex cells that are capable of numerous biologic activities and yet that seem fairly independent of other systems of the body. In a broad sense their functions include phagocytosis of exogenous and endogenous particles, analysis and digestion of the same, and either excretion of the products of digestion or elaboration of new products to meet the needs of the body. They serve in the conservation of iron from effete erythrocytes and in pyrrole metabolism. They probably take part in the intermediary metabolism of lipids. Their synthetic capacities involve processes of immunization; they probably involve elaboration of certain of the lipo-proteins necessary to the body; and they may involve elaboration of other biologically active combinations of protein with other constituents. Investigation of these capacities and of the forces that attract to R-E cells substances which may then be destroyed or from which the cells can elaborate useful new products should expose entrancing revelations. These should prove to be valuable links to numerous disease processes and to many of the remarkable findings that biochemists are contributing concerning the constituents of tissue extracts.

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Hypo-Ovaria—Diagnosis and Treatment

Grace T. Newman, M. D.

IN HYPOFUNCTION of the ovaries, we have a clinical syndrome caused by insufficient estrogen production, starting in the early thirties, and continuing into the forties. Just as the thyroid has symptoms due to the insufficient production of thyroid secretion, so the ovaries have symptoms due to the insufficient production of estrogen. Since errors are frequently made in diagnosing this condition as a neurosis or a state of nervous exhaustion, or in confusing it with hypothyroidism, this article is an attempt to bring the syndrome to the attention of the general practitioner.

The advent of the study of vaginal smears has proved a valuable and simple method of diagnosing the condition. By the use of the smear, it is possible accurately to study the ovarian function by the response of the vaginal epithelium to the estrogen produced by the ovary. These changes were first noted by Papanicolaou[1] and later described by other workers in the field of endocrinology.

I use the Shorr[2] method of staining the vaginal smears as I find it a simple and excellent staining medium. The use of the vaginal smear, as an aid in the diagnosis of endocrine problems in women, I have discussed in a previous article.[3].

The ovary has a double function. Primarily, it produces ova and the corpus luteal hormone which aids in gestation; and secondly, it produces estrogen which is responsible for the secondary sex characteristics and profoundly affects the nervous system, circulation, and body processes.

There are two types of estrogen deficiency. A primary type occurs in adolescence and leads to imperfect development of the genital organs, especially the uterus which persists as an "infantile type." Patients with this type of deficiency are usually tall and slender with lower extremities and arm span long in proportion to the length of the trunk. This primary deficiency may be constitutional or hereditary, or it may be due to a primary deficiency of the anterior lobe of the hypophysis, sex glands, or thyroid. The secondary type is due to such various causes as psychic or physical trauma, infections, or related disturbances in the other glands of internal secretion. The deficiency due to reduction or lack of estrogen leads to a group of symptoms and physical findings. The age at which this most frequently occurs is between 30 and 40. In my experience, it has been more frequently seen in married than in single women.

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The important part that estrogen plays in the mental and physical being of a woman is frequently ignored or overlooked. The sense of well-being that exists during pregnancy is undoubtedly related to the large production of estrogen at that time. In endometriosis, where is found an over-production of estrogen due to overactivity of the ovaries, the patients are in good physical health except for the symptoms caused by the endometrial implants. I have observed in many patients of the age group 45 to 60 years that those who have very few menopausal symptoms are the ones who show signs of continuing ovarian activity as seen by study of their vaginal smears. This activity may persist for years after the cessation of menses.

Estrogen affects not only the female genital tract but also other epithelial structures, as the epidermis and the mucus membranes of the nose, throat, and eyes. In the skin, where there is estrogen deficiency, we see dryness and lack of tone, and in the mucus membranes, atrophy or congestion. Estrogen also affects the mental outlook.

The chief symptom of hypo-ovaria is usually fatigue, even to the point of complete exhaustion, depending upon the severity of the deficiency. The previous health has usually been

good and there is no history of nervousness. There is a tendency to be forgetful and a definite loss of the ability to concentrate. With this is a feeling of nervousness and uncertainty and at times considerable tension. There may be various head complaints, described as a dull feeling in the head or a feeling of pressure or tension in the back of the head and neck. At times there is backache or other aching in the joints. Sleep disturbances are quite common and are usually described as an awakening between two to four in the morning, after having gone to sleep immediately upon retiring. The early awakening is not followed by further sleep until after two or three hours of wakefulness. The patient frequently complains of restlessness during the night. A sensation of floating or light headedness frequently is described. Gastro-intestinal symptoms are not prominent but, if present, may be nausea or constipation. Frequently there is loss of libido. Mental depression is present, but in degrees depending upon the severity of the deficiency. The menstrual periods are scantier, have become irregular, or are completely absent.

On physical examination, one notes a skin which lacks tone, is frequently dry, and in some instances has a tendency to scale and to show areas of dermatitis. The hair lacks tone. The blood pressure is often on the low side. The pelvic examination may reveal mild displacements. Frequently we find an accompanying endocervicitis which may be one of the contributing causes of the condition. The majority of the patients have had one or two children. It is not uncommon for the condition to follow childbirth.

The vaginal smears show evidence of a deficiency of estrogen production. Geist and Salmon[4] have noted the following cellular changes in the smears.

1. Advanced estrogen deficiency; pus cells and atrophic cells, with no squamous cells present.

2. Moderate degree of estrogen deficiency; various number of epithelial cells irregular in shape with large nuclei; some atrophic cells and leukocytes.

3. Slight degree of estrogen deficiency; large irregular epithelial cells with irregular outlines, plus clumping. There may be a few deep cells or large squamous (cornified) epithelial cells with small deep nuclei.

The chief finding is a decreased number or a complete absence of cornified cells throughout the cycle.

In looking over the histories of 20 patients, I find that in 17 the age ranged from 25 to 40 years; 3 patients were 42. Nineteen of the patients were married; 1 was single. Six patients had had no pregnancies; 7 had had one child; 7 had had two or more. Ten had had previous operations on pelvic organs of which 6 were operations to resect or remove the ovaries.

Irregular or scanty periods occurred in all cases; 4 patients had amenorrhea. Dizziness was mild in the majority of the cases, 14 out of 20. Headache was moderately severe in 8 out of 20; severe in 5 cases. Exhaustion was severe in 13 patients and moderate in 6 cases. Nervousness was marked in 11 patients and moderate in 8. Emotional instability was on the moderate side. Mental depression was slight in the majority of cases. Poor sleeping occurred in almost half of the cases. Loss of libido was noted by half of the patients. The blood pressure was normal in 14 and low in 6. The pelvic findings showed mild displacements in 3 patients, endocervicitis in 3 cases. In the rest of the group there were no demonstrable disease conditions on local examination.

Differential Diagnosis

This ovarian deficiency is frequently confused with an anxiety neurosis, hypothyroidism, or the menopause.

In the anxiety state, we find an individual with cold clammy hands who complains of some or all of the following symptoms; palpitation, shortness of breath, tremors of the extremities, nervous indigestion, constipation or diarrhea, occipital headache or tightness in the head as though a tight band were encircling the head. There is always an underlying fear complex.

In thyroid deficiency, we find complaints of fatigue beginning in the morning, frequent headaches, constipation, mental sluggishness, irritability, coldness of the extremities, slow pulse, and low metabolism.

In the menopause we have an older age group. Vasomotor disturbances along with varying degrees of emotional disturbance and mood depressions are diagnostic.

Treatment

These patients cannot be treated haphazardly with an occasional injection of an estrogenic preparation. The dosage varies and must be tried out, and the responses studied clinically and by vaginal smears. I do not routinely do daily smears, be-

cause of time and expense, but I do check the smear 5 to 7 days after the menses are over and premenstrually.

Normally the production of estrogen reaches a peak in the middle of the cycle and again there is a slight rise just before the menses begin. Many women will normally show mild symptoms due to low estrogen premenstrually, such as loss of energy, irritability, restlessness, and mild depression. Therefore, we usually find the signs of ovarian deficiency exaggerated premenstrually or immediately following the menses.

In consideration of these factors and in order not further to depress the function of the ovaries themselves, we give the largest dose the last half of the cycle. Brown, Bradbury, and Jennings[5] found that giving estrogen as stilbestrol, 10 mg. daily by mouth the last half of the cycle, did not affect the luteal phase but when given continuously throughout the cycle in a dosage of 3 mg. daily it inhibited ovulation. A small dose is given from the end of menses up to 14 to 18 days from the first day; then the dose is increased for 7 to 12 days, and discontinued a few days before the period is due. The medication can be used by mouth or injection as the results are comparable.

The following are some of the drugs and their dosages which I have used successfully:

1. Estradiol benzoate by injection, .333 mg., as two injections weekly to the mid-cycle; then 0.84 mg. to 1.66 mg., three times weekly for another 10 days.

2. Monomestrol by mouth, 2.5 mg., from the end of the menses up to 14 days from the first day; then 5 to 10 mg. per day for 12 days.

3. Conjugated estrogen by mouth, 1.25 mg., from the end of the menses up to 14 days from the first day; then 2 to 4 tablets of 1.25 mg. each, for 12 days.

4. Dienestrol by mouth, 0.5 mg. per day from the end of the menses up to 14 days from the first day and then 2 to 3 tablets of 0.5 mg. each, for 12 days.

In the patient with amenorrhea or very irregular periods, a selected dose such as conjugated estrogen 3. to 1.25 mg. tablets daily, are given for a period of 21 days with a rest interval of one week. Should the symptoms be severe postmenstrually a small dose is given during the menses.

Occasionally there is a delay in onset of the period, at times due to overdosage or to error on the part of the patients. Should this occur, I give one or two doses of progesterone by injection in dosage of 25 mg. each dose. This brings the period on within a few days.

The following is a brief report on the case history of one of the patients:

The patient, Mrs. R. P., a 34-year-old housewife was first seen by me on January 19, 1943. At that time she was complaining of dizziness, or of a floating sensation in her head associated with frontal headache of a mild degree. She tired easily, had a poor appetite, suffered from constipation, was unstable emotionally, and mildly depressed and irritable at times. All the symptoms were exaggerated premenstrually. Her menses for the preceding year lasted only one day, instead of her usual three, and were coming every 21 to 25 days. She had one child 10 years of age. Three years after this pregnancy she had had a pelvic operation with the removal of a cyst from the right ovary. The vaginal smears when first seen and subsequently showed a deficiency of ovarian function. Her physical examination showed a skin which was dry and lacked tone; the hair was also lifeless; she appeared apathetic. The blood pressure was normal, as were the other physical findings. Basal metabolism was 1 plus. Barium enema showed a normal colon.

She was given, at the beginning of treatment, injections of estradiol benzoate 0.333 mg., three times weekly the last half of the cycle. With this there was considerable amelioration of her symptoms. She began to take more interest in doing things and there was a great lessening of her fatigue and nervousness. In June, 1943, she was placed on oral medication in the form of conjugated estrogens with a dose of two tablets of 1.25 mg. each from the fourteenth day of the cycle for a 12-day period. Later she was given one pill from the end of the menses through the fourteenth day. This dosage has been varied slightly; at times it has been increased to 3 tablets daily the latter half of the cycle. For the past 3 months, she has taken 2 conjugated estrogen tablets of 1.25 mg. each, from the end of menses to 18 days from the first day, then 5 per day for 7 days.

There has never been a period delay and the cycles come every 26 to 28 days with a 2 to 3 day scanty flow. The vaginal smears have never shown any signs of overdosage. The pelvic organs, as well as the breasts, appear normal.

When seen on February 9, 1949, she complained of no symptoms except a feeling of laziness and slight mental sluggishness for a few days premenstrually. Her appetite is good, and her bowels move regularly. She is carrying on an

active program in her church and with the Parent Teachers Association, as well as studying voice culture. She looks well, and her hair and skin have a fresh, youthful appearance.

All the 20 patients in this series are still under observation, the length of time varying from 1 to 12 years; 66 percent have been under observation over 4 years; the balance 1 to 3 years; 90 percent have shown full recovery or definite relief of symptoms; 10 percent have not shown improvement.

Summary

This article is an attempt to bring the attention of the general practitioner to the recognition and rational treatment of the syndrome of hypo-ovarianism which we see both as a mild and as a severe deficiency. The vaginal smear is a great aid in its recognition. From a practice devoted chiefly to gynecological problems, I have selected twenty patients at random who presented similar symptom complexes and who responded to treatment with estrogens used cyclically. These patients fall chiefly into the age group of 30 to 40 years. The majority had had one or two children. A certain percentage gave a history of operations upon the ovaries, with some subsequent period irregularities and scantier menses. The chief symptoms are fatigability, nervousness, dizziness, headache, mood variations, and poor sleeping. The condition is often temporary and the symptoms can be held in practically complete abeyance by the use of estrogens. The length of time of treatment may be months or even years as it is in any glandular deficiency. The haphazard use of estrogen has caused physicians to feel they were dealing with a neurotic patient. The nervousness is not that of an anxiety state and there is not the underlying emotional instability and unbalance. The relief of this nervousness by estrogen, in my experience, is a well-established fact.

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Current Opinions on the Use of Low Sodium Diet in Hypertension

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KEMPNER'S STUDIES of patients with renal metabolic dysfunction,[1] and later of many patients with hypertension[2] treated with the rice diet, have stimulated thought and further studies. Observations of such patients, both on the rice diet (which Kempner believes has special efficacy per se—not alone because of its low sodium content—in the lowering of blood pressure in some patients) and on diets low in sodium but much less restricted in protein content, have been made by several investigators in the past five years.[3, 4, 5, 6, 7]

Diets low in salt have been used for many years[8] in the treatment of hypertension. It was at first thought that restriction of the intake of chloride was responsible for the decline in random blood pressure readings in some of these patients. It is now generally conceded, however, that the sodium ion is the one more intimately concerned with water balance, and that restriction of sodium intake will significantly lower blood pressure readings in a certain percentage of patients with hypertension.

Perera, in carefully controlled studies on patients with normal cardiac and renal function, has recently shown[9] a small, but significant, decrease in early morning blood pressure readings in a group of hospitalized hypertensive patients in response to diets containing only 0.2 to 0.25 Gm. sodium. No change was noticed in random blood pressure readings on these patients though the "resting" blood pressure was consistently lower.

Stead, Reiser, Rapoport, and Ferris[10] at the University of Cincinnati also studied a series of 12 hospitalized patients with severe persistent hypertension. Severe sodium deprivation (diets containing 0.2 to 0.25 Gm. sodium or 0.5 Gm. sodium chloride) was carried out, with alternate "salting" and "desalting" periods, which lasted from 7 to 21 days. In eight patients a mercurial diuretic was administered once to three times weekly, during "desalting" periods; then the mercurial diuretic was discontinued and 2.4 Gm. sodium chloride in enteric coated tablets was given without a change in diet for from 7 to 12 days. Patients were not told of any changes in regime.

Six patients with no determinable impairment in renal function were watched through several alterations in sodium balance so that the consistency of the response could be noted. Serum sodium level was determined in seven patients at the height of the desalting and again in the high salt intake period. Five of these patients consistently showed a fall in random blood pressure readings during the desalted periods as compared to the salted periods. In four, however, the random systolic blood pressure declined while no significant change occurred in the diastolic levels.

Schroeder[6] studied the effects of the rice diet on seven patients hospitalized for relatively long periods of time. He compared the findings with the changes in blood pressure readings induced by salt restriction and those occurring without

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specific treatment other than hospitalization. These patients were hypertensives and had normal blood nonprotein nitrogen levels. They were willingly hospitalized for minimum periods of 3 months. A control period of from 21 to 51 days preceded specific dietary treatment, so that changes in blood pressure associated with hospitalization and rest alone could be evaluated.

The rice diet (as prescribed by Kempner) was then administered for from 16 to 90 days. The sodium content did not exceed 0.2 Gm. Ferrous sulfate and multivitamin supplements were given. The results of this regime were compared with those expected from restriction of sodium alone, in three patients. In discussion, Schroeder[6] states that "a rough estimate can be made that the blood pressure of only about 10 percent of an unselected group of patients with well established hypertension will fall to normal under the influence of a diet restricted only as to salt." This conservative estimate varies from Kempner's published results with 271 patients without evidence of renal involvement treated by the rice diet over periods from 4 to 898 days. He says that 67 percent were improved, 33 percent not improved. One notes that Schroeder reported those patients whose blood pressure returned to normal, while Kempner's criterion for improvement of this one factor was a significant fall on "mean" arterial pressure. However, Schroeder, who also studied patients on the rice diet, concludes (cited above): "A diet of unsalted rice, fruit juices, and vitamins is of questionable value in the treatment of most patients with hypertension, and changes in blood pressure occurring in other patients after restriction of sodium chloride alone were of similar magnitude to those observed with the use of the rice diet.[3] Similar changes have occasionally occurred following hospitalization alone without alterations of diet." His experience leads him to believe that neither salt restriction nor the rice diet will be efficacious in advanced cases.

In a panel discussion in the Scientific Session of the American Heart Association, June 4, 1949,[11] Schemm remarked that the psychological value of the rice diet, administered hopefully and with conviction in surroundings especially suited to its enthusiastic reception, cannot be underestimated.

Schroeder, also, states that the rice diet is "very low in protein and fat, very low in salt, and has strong psychotherapeutic influences."

Until recently little has been known about the physiological mechanisms involved in the maintenance of blood pressure. With the advent of tetraethylammonium chloride, a drug is at hand which causes transient block of autonomic ganglia.[12] Investigation of its properties have been made by several groups of workers,[10, 12, 14, 15, 16] and the results observed following intravenous administration in both normotensive and hypertensive individuals, and in non-pregnant and pregnant women.

Physiologists and clinicians have attempted to understand the multiple means whereby blood pressure levels are maintained in health, and why they rise or fall in disease and in response to emotion or drugs. Schroeder considers that four simple mechanical factors act to maintain a normal blood pressure, or a high one: the volume of blood, its viscosity, the function of the heart, and the resistance to blood flow in the periphery. He maintains that "the blood pressure can be considered as a resultant of a number of interacting influences, and can become decompensated in a number of ways. It may be as untrue to state that all cases of arterial hypertension have the same basic disturbance as it is to state that all patients with fever have the same etiologic agent."

Fishberg[13] describes essential hypertension as a "collective concept for a number of conditions having in common the positive characteristics of arterial hypertension and the negative one of the absence of primary renal disease."

Stead and his co-workers present the following hypothetical picture of the maintenance of peripheral resistance.[10] "The blood pressure at any time reflects the total effect of the humoral and neurogenic factors operating, plus whatever intrinsic tone the vascular bed may possess."

Perera believes that sodium deprivation diminishes the basal humoral component in blood pressure. But he interprets the lower morning readings in his series of hypertensive patients on low sodium diets[9] to mean that the neurogenic tone is lower after rest, and rises as the patient meets the demands of the day. Certainly it is now obvious that not all cases of high blood pressure have the same etiology.

By the use of TEAC, Ferris and his co-workers have attempted to evaluate "the relative roles of neurogenic and humoral tone in the maintenance of blood pressure in health and disease."[14, 15] They recognize several physiologic variants of clinical hypertension, including "in-

trinsic" tone or the basal blood pressure. With TEAC used in supine subjects they state: "If one assumes the blockade (of autonomic ganglia) is complete under the influence of the drug, the fall in blood pressure resulting when it is given is that of the neurogenic component, and the resulting pressure at the height of the effect of TEAC represents the level maintained by humoral factors and the intrinsic tone of the blood vessels as manifested by the peripheral resistance." The action of humoral pressor agents such as angiotonin or epinephrine is not prevented by TEAC ganglion blockade or autonomic paralysis of other types. This investigation presents evidence that the hypertension occurring in toxemia of pregnancy and in acute glomerulonephritis is humoral in origin. In so-called essential hypertension either of the two factors, neurogenic or humoral, may be the predominant one in sustaining the elevated pressure, or both factors may be present in varying degree and be interactive.[15]

Stead, Reiser, Rapoport, and Ferris have attempted "to define, if possible, the physiological mechanisms concerned in the changes associated with drastic shifts in sodium balance." They have observed the effects of salt balance on random blood pressure readings and also on the response of blood pressure to the TEAC ion. Five patients without renal impairment showed significant responses in the lowering of the TEAC floor while on strict sodium restriction. In a group of seven patients with malignant hypertension, renal failure, or both, no significant change occurred in random blood pressure, TEAC floor or TEAC response. Schroeder confirmed these results when he concluded[6] that in patients with advanced hypertensive disease the use of the sodium regime produces no changes of real benefit.

Changes in sodium balance probably alter blood pressure by lessening the humoral component. If the renal function is adequate, sodium can be conserved and maintained in isotonic concentration in the blood even on a vigorous desalting regime. In patients with severe renal damage or malignant hypertension there may be an inability to conserve electrolytes as the only manifestation of renal damage. In chronic nephritis such an inability is observed.[10]

In patients with such impairment of renal function an apparently large humoral component in peripheral resistance may be uninfluenced by very severe sodium restriction. It is in this group of patients that some fatalities have occurred when sodium is severely restricted. These patients had lower control sodium levels and changes were greater than in patients with little or no discernible restriction in renal function, although sodium restriction was less. In other patients there has been no correlation between the clinical condition, blood pressure levels, and serum sodium concentration.[6, 10]

The endocrine factors in blood pressure changes have also been studied. Goldblatt[17] reports: "Of the endocrine organs, the only one that may possibly play a significant, even if only a secondary, part in hypertension is the adrenal, although this conclusion is contested on the basis of inadequate evidence."

There is considerable knowledge of sodium balance in its relation to Addison's disease and other adrenal cortical disorders where loss of sodium chloride is responsible for many of the symptoms of the condition.

Perera[18] believes that there is considerable evidence that the adrenal cortex plays a part in the regulation of blood pressure levels. Certainly the elevation of blood pressure in the presence of adenomas of the adrenal cortex is well known, as is the association of hypotension with hypoadrenalism. In some patients with this condition Perera[18] and Knowlton[19] found that desoxycorticosterone was capable of producing hypertension. Perera is quoted thus: "The fact that desoxycorticosterone has pressor potentialities raises the question whether the abnormal liberation of certain adrenal cortical hormones may be concerned in the etiology of hypertension even though consistent anatomic change is not apparent."

Schroeder[6] also noticed that, in his studies with a low sodium diet in hypertension, the successful results often occurred in obese women of about menopausal age or in those who had menstrual disturbances. These patients often had obesity confined to the trunk and showed a mottled cyanosis of the extremities. They often exhibited abnormal glucose tolerance curves resembling those seen in diabetics. They also occasionally showed hirsutism. He suggests that "these patients clinically present the possibility that the adrenal cortical activity is altered, with secondary associated hypertension."

Case Reports

It is difficult, indeed, to keep uninstitutionalized patients on either the rice diet or on a diet re-restricted to less than 0.5 Gm. sodium daily. Twelve hypertensive patients with unimpaired or only slightly impaired renal function were persuaded to attempt such an effort while continuing their usual activities. Of these, seven discontinued the diet before conclusions could be drawn. (Three of these, rather emotional women, became quite depressed and agitated after only a few days on the diet and refused to try it any longer.) Three were unco-operative and too spasmodic in their attempts to stay on the diet to draw conclusions as to its benefit for them. One patient died of cerebral hemorrhage before conclusions could be drawn. One failed to return frequently enough for adequate data to be obtained. This left four patients who co-operated whole-heartedly and adhered to the low sodium diet for weeks, or months, returning as directed for blood pressure readings.

PATIENT 1. M. A., a 42-year-old white woman, known and followed since 1940, had blood pressures during 1940 ranging from 200/120 to 186/90. At that time her urine contained albumin (1 plus) and on occasion hyaline casts; the specific gravity was 1028. She had had a toxemia of pregnancy in her only pregnancy ten years previously, but urine examination and blood pressure readings were not done following her delivery. She weighed 150 pounds; her height was 61 inches.

In 1946, when she was 49 years old, she was still menstruating, with menorrhagia for 1 year. She was admitted to University Hospital, Cleveland, Ohio, as a possible candidate for thoracolumbar sympathectomy. Though she had no symptoms attributable to her high blood pressure, random readings in the previous two years had ranged from 250/140 to 234/120. For two months before hospitalization testosterone 50 mg. weekly was given in an effort to control the menstrual bleeding.

There was some silver wiring of the retinal arteries; no hemorrhages or exudates were seen. On admission the blood pressure was 260/130; urine was normal; blood urea nitrogen was 13.5 mg. per 100 cc.; the serum proteins were normal; cholesterol was 220 mg. Intravenous pyelograms showed a normal urinary tract.

Amytal test was done, at which time the blood pressure dropped to 160/124. The cold pressor test was done on the same day. During immersion in the water, the systolic blood pressure rose 30 to 40 mm., the diastolic, 10 to 30 mm.

The patient wished to try the rice diet as used by Kempner. This was begun December 15, 1946, and augmented by ferrous sulfate and multivitamin capsules. She was observed regularly and after 4 weeks the diet was supplemented by lonolac. On January 16, 1947, the pressure was 230/130, and finally after 8 weeks fell to 202/120. The weight dropped to 146 pounds. Sodium restriction to 0.5 mg. daily was carried on until September 30, 1947, during which period the blood pressure readings rose again to 230/140. At that time she was placed on a normal diet, as X-ray therapy was started to combat the menorrhagia.

PATIENT 2. Mrs. E. U., a white woman, was first seen in 1945 when she was 65 years of age. Several blood pressure readings at that time ranged from 170 to 160/100. The urine was normal. During the following 2 years the blood pressure rose to 190/110, then to 204/114, concomitant with a weight gain of 15 pounds to 165 pounds. On October 10, 1948, she was placed on 0.25 mg. sodium daily with lonolac to give milk proteins. She was very faithful in her adherence to the diet. In six months she was seen seven times. The weight fell to 158 pounds and the blood pressure readings came down within three months to 162/90, then in six months to 160/84. At the onset of hot weather, May 13, 1949, she was given regular bread and whole milk to raise the sodium content of her diet.

PATIENT 3. D. T., a white man, age 45 in 1943 when first examined, had several blood pressure readings of 184/120 to 170/110. He was seen again in 1946 with readings of 212/136 to 200/124. At this time he was smoking 50 cigarettes a day and drinking about 10 to 16 ounces of whiskey daily, with usually a very inadequate evening meal, but a fairly good breakfast. With sedation on triple bromide and phenobarbital, reduction of cigarettes to 12 daily and of whiskey consumption to 4 to 6 ounces daily, and an adequate diet daily, the blood pressure gradually came down to 190/120, and after a vacation, to 180/112. Wolpaw reported well advanced vascular sclerosis of retinal vessels with marked thickening of the vascular tree with plus 2 venous indentation. No hemorrhages or exudates were seen. The urine was normal. In March 1948, when pressure of business was intense, the blood pressure rose to 224/130 and tachycardia was up to 120 per minute. After 7 weeks of a trial of testosterone, 25 mg. intramuscularly 3 times weekly, the dose was reduced to 25 mg. every 7 days; the readings were 204/120 to 200/118. When no further lowering occurred, a low sodium diet was begun April 20, 1948, (0.5 mg. sodium daily). In 4 weeks the blood pressure fell to 176/110 and on June 7, 1948, was 166/100. He then took two months' vacation and went on a normal diet. On his return, September 7, 1948, the reading was 176/100, on November 15, it was 206/110 and on February 18, 1949, it was 194/120.

PATIENT 4. Mrs. D. T., the wife of Patient 3, had been under regular observation since 1930. In 1933, a cholecystectomy was done for stones. Her health was otherwise excellent. In 1939, at the age of 42, an attack of pyelocystitis occurred, during which her previously normal blood pressure rose to 160/120. With neoprontosil administration and clearing of the urine, the blood pressure fell to 144/110. After a second urinary tract infection 9 months later, the blood pressure was 180/120 and continued close to this figure until late 1942 when it varied on several occasions. By early 1943 it had risen to 212/140 and menopausal symptoms were present. The urine was normal. During the next 2 years 21 random blood pressure readings were done. The highest was 230/140, the lowest 178/118. During this time she received some estrogen orally, with occasionally an added amount intramuscularly, when menopausal symptoms were severe.

In 1945, on potassium thiocyonate, because of severe headaches, readings were reduced significantly, the lowest being 164/110. Blood levels were closely watched and medication discontinued several times over a period of 24 months, then discontinued entirely as headaches were not severe.

Low sodium diet was begun April 20, 1948, at which time the blood pressure was 220/120. It was unchanged over a period of 7 weeks during which time the diet was conscientiously followed. The diet was discontinued after 8 weeks.

Conclusions

We agree with Schroeder, Grollman, and others that: 1. Only a small percentage of hypertensive patients are emotionally stable enough to stick to a rigorous salt restrictive regime. 2. Of those who do persist, from 10 to 20 percent only will have significant falls in blood pressure. 3. If the patient has symptoms attributable to hypertension, and little or no renal damage, and is willing to try such a rigid schedule, a diet restricted to less than 0.5 Gm. sodium daily may reduce his systolic blood pressure significantly. Reduction of the diastolic reading is less likely to occur.

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Internal Medicine

THE THIRTIETH ANNUAL session of the American College of Physicians was held in New York, March 28 through April 1, 1949. Morning lectures, hospital clinics, and panel discussions were on topics of interest and of practical value to all physicians. In the general sessions, a wide range of subjects was covered some of which are herewith briefly reported.

DIAGNOSIS AND MANAGEMENT OF ATYPICAL OR VIRUS PNEUMONIA: John H. Dingle, Professor of Preventive Medicine, Western Reserve University School of Medicine, Cleveland, Ohio—In the past ten years over 300 papers have been published on atypical pneumonia. It was first brought out as an entity in 1937 when treatment with the sulfonamides demonstrated a group of pneumonias which did not respond to these drugs. It is characterized by great variation in signs, symptoms, and severity, and must be differentiated from a long list of diseases other than bacterial pneumonia. Incidence is about one case per thousand persons per annum, or about ten times greater than bacterial pneumonia. The diagnosis is largely by exclusion, although a rise in the cold agglutinins may be helpful. There should be attention to the following considerations: *Isolation:* In one series 83 cases occurred in 19 families (The incubation period is 2 to 3 weeks). *Specific therapy:* Aureomycin is now being reported as effective; the sulfonamides and penicillin are of no benefit; streptomycin has been reported as useful in several cases but is not generally so.

BLASTOMYCOSIS (IMMUNOLOGIC TYPES): David T. Smith, Professor of Bacteriology and Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C.—Twelve species of blastomyces exist, of which six are of major importance for man. In only three of these are immunologic methods applicable: *histoplasmosis,* distributed through the midwest states; *coccydiomycosis,* occurring largely in the southwest; and *blastomycosis,* which is widely distributed throughout the United States, including the southeast. Three types of immunologic reaction are present and determine the type of treatment: the skin may be positive with a negative complement fixation; or the reverse; or both may be negative. If all are negative the patient should be vaccinated to raise resistance before treatment with potassium iodide is begun, otherwise wide dissemination of the disease may occur.

TREATMENT OF SYPHILIS: L. Earle Moore, Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.—The incidence of syphilis has been declining since the war and is now approaching the 1942 level. This is probably due to early treatment with penicillin as well as to the demobilization of troops. The advent of penicillin, especially the long acting varieties, has made treatment an office procedure. There is danger, however, in restricting treatment merely to injections given by the office nurse, for the psychology of this kind of patient requires careful handling and social and economic implications need to be explained. 1. *Early syphilis:* a total of 6,000,000 units in a total of ten treatments should be given, and be followed by physical examination at monthly intervals for a year, then at intervals of three months, and then yearly, for there is failure in 15 percent to 20 percent and relapse may occur within 18 to 20 months. The results of re-treatment are not so good as in the primary series. If the serologic reaction does not revert towards normal or remains at 50 percent of the original titer, re-treatment should be given. 2. *Prenatal syphilis:* This is easily cured by penicillin. One hundred percent of cases are cured by treatment of the mother during pregnancy. 3. *Latent* or *non-symptomatic syphilis:* One should be certain that it *is* asymptomatic, and also that syphilis is really present as a positive reaction may be due to 40 other conditions (including atypical pneumonia). This phase should be treated in the same manner as the original schedule. Penicillin is not effective in reversing the serologic reaction in latent lues and we shall not know for another generation how effective it is in controlling clinical syphilis. 4. *Late syphilis:* the penicillin range should be from 4,000,000 to 10,000,000 units over a period of 10 days to 2 weeks; 4a. *Cardiovascular lues:* No Herxheimer reaction of serious

consequence has been seen by the author and since it is an "all or none" reaction nothing is gained by giving under 10 units per kg. The ultimate outcome here, too, is not known. 4b. *Central Nervous System Lues:* Penicillin is better than the old therapy of arsenic and bismuth; the chief question is whether to combine with it fever therapy. This the author gives if the disease threatens life, vital function, or sanity, as in dementia paralytica or in optic atrophy.

PREFRONTAL OPERATIONS FOR THE TREATMENT OF MENTAL ILLNESS: J. Lawrence Pool, Professor of Neurological Surgery, Columbia University College of Physicians and Surgeons, New York, N. Y.—These operations consist either of resection of portions of the white matter of the frontal lobes or of the gray matter, and experience has shown that bilateral surgery is necessary to give satisfactory results. The operations are done anterior to the coronary suture, the most radical as to loss or blunting of personality occurring as a result of trephining and resecting a wedge of gray matter in the frontal lobe. Less radical procedures, resulting in less change of personality but successful in restoring normal or improved mental conditions, are obtained by undercutting either through trephine incisions or through the transorbital route, going through the upper margin of the orbit and "ice-picking" the white matter from below. This is a relatively simple procedure for the patient, who is usually up and about within an hour or so. Consultation must be had with psychiatrists to decide what type of operation to use in the individual patient, and results depend largely upon the severity of the psychosis and deterioration present. As would be expected, the dementia præcox patient responds least well, and of this group the earlier the case and the less seriously involved the better the response. The conditions which are best suited to these procedures are the involutional depressions and the other affective types, often with suicidal trends, as well as the simpler obsessive and compulsive groups. Mortality rates, depending on the type of surgery done, vary from 1 percent to 5 percent. Complications which arise are not of serious nature; in 7 percent to 11 percent convulsive seizures occurred, but in some of these convulsions also were present preoperatively. In two of a series of 54 cases hematoma following operation occurred but was successively relieved. Incontinence of urine has been reported.

DIETARY INVALIDISM: Henry J. John, Physician, Lakeside and St. Luke's Hospitals, Cleveland, Ohio—It was pointed out that in certain diseases in which the diet is a large factor in the treatment, more harm can come from the diet than from the conditions treated. Among these are diabetes, food allergy, functional hypoglycemia, hyperthyroidism and other conditions in which it is not uncommon to find glycosuria although a true diabetes is not present. Overeating was considered one of the most serious of health problems. In a series of 6000 cases of diabetes, 52 percent to 69 percent of the patients were overweight. In diabetes, in particular, often simple weight reduction with qualitative carbohydrate restriction will control the disease. A high incidence of degenerative diseases occurs among the obese. Reduction diets should be strict (not over 900 calories) but simple, omitting chiefly sugar, pastry, and soft drinks, but otherwise allowing a general diet so that the family routine will not be disturbed.

RESEARCH IN CORONARY HEART DISEASE: Paul D. White, Clinical Professor of Medicine, Harvard Medical School, Boston, Mass.—This paper was introduced by the comment that the attitude of the profession with regard to this disease was one of apathy and fatalism in view of the complexities and difficulties of the problems to be solved. The paper consisted of an outline of the field to be covered in the next 10 years, and 75 questions were asked based on problems of heredity, anatomy, and physiology. A list of drugs in common use was given and the mechanism of action presented as open to re-evaluation.

LOWER NEPHRON NEPHROSIS: William Goldring, Associate Professor of Medicine, New York University College of Medicine, New York—This condition is seen in so-called "crush syndrome," transfusion reactions, and postoperative shock, and in certain poisons. It is characterized by oliguria or anuria, which if continued over two to four hours produces irreversible damage to the kidney especially to the distal tubule. The immediate cause is vasoconstriction of the renal artery in an effort to divert blood in emergency to more vital organs. The biochemical changes were described and treatment outlined, with emphasis on early recognition of the condition and the judicious use of infusions, using care not to "drown" the patient in an effort to restore blood volume and re-establish renal circulation.

CLINICAL SIGNIFICANCE OF CRYOGLOBINEMIA: David P. Barr, Professor of Medicine, Cornell University Medical College, New York, N. Y.—Definition of the term: globulin precipitated at room temperature ("cold" globulin), hitherto un-

detected, since the protein falls with the red blood cells and so escapes detection in the supernatant fluid. Two cases were reported from the New York Hospital; the first, one of purpuric eruption which disappeared with warmth; the second, a case of multiple myeloma with Raynaud's syndrome. The globulin was isolated and studied as to physical properties. It was found to have a distinctive electrophoretic pattern, the first globulin to be so identified. This material was produced in great quantity by the patient with multiple myeloma and was seemingly a product of the plasma cells. On autopsy the plasma cells in the bone marrow stained identically with the globulin. Study was made of 100 ill patients in the hospital (ill of many varieties of disease) and of 40 normals. Twenty-five percent of the former showed the presence of this protein, and none of those in the control group. Speculation was offered as to the significance of such easily precipitated protein in the etiology of many diseases, such as purpura, allergy, rheumatic fever, Buerger's disease, Raynaud's syndrome, and similar conditions in which obstruction of the small capillaries or arterioles may significantly alter or determine the course of the disease.

Clinical Angiocardiography: Israel Steinberg, Instructor in Radiology and Medicine, and Charles Dotter, Instructor in Medicine, Cornell University Medical College, New York, N. Y.—X-ray films were shown to demonstrate the value of definite diagnosis made possible by this method in cases of congenital heart disease, especially those amenable to surgery; also accurate diagnosis in differentiation of mediastinal tumors, bronchogenic carcinoma, and syphilitic aortitis or aneurism.

Pheochromocytoma: George F. Cahill, Professor of Urology, Columbia University College of Physicians and Surgeons, New York, N. Y.—The site of these tumors, chiefly upper abdominal, in or around the adrenal gland, or occasionally in the chest, was brought out, in the former group to justify the surgical approach by transverse upper abdominal incision since these tumors are not infrequently multiple. The characteristic symptoms of paroxysmal hypertension, pain, rise in blood sugar, and rapid pulse rate are the most outstanding. Diagnosis is made possible by response to benzydioxane (an antagonist) which causes drop of blood pressure during the attack, or by dibenamine hydrochloride which may cause a prolonged drop lasting for 24 hours and which may prove to be useful in preoperative preparation. The prognosis for cure is excellent, since the tumor is rarely malignant. But the operative risk is great; the risk, however, is decreasing as a result of better preparation of the patient and of supportive measures during the operation. The operative risk now stands at about 16 percent.

Treatment of Heart and Kidney Disease and of Hypertensive Vascular Disease With the Rice Diet: Walter Kempner, Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C.—The use of the rice diet unless properly done may be both ineffective and dangerous. Controlled studies should be made of blood chemistry, eyeground changes, electrocardiographic studies, etc. The diet is ineffective unless strictly adhered to in detail. The Kempner diet contains less sodium and less chloride than any similar diet advocated for the same purpose, also, less protein and cholesterol. Changes must be made to meet the changing situation in body weight. The protein elements of the diet are in general superior in quality. An individual on this diet does not develop anemia and there is a decrease in nonprotein nitrogen and urea as well as in the cholesterol levels. Values for sulphates and phosphates indicate that there is no breaking down of endogenous protein. The average duration of treatment, in a series of 490 cases of hypertension which responded satisfactorily, was from 3 to 4 months, the shortest time being 4 days. Cases were cited showing not only marked reduction of blood pressure to normal levels but changes in arteriosclerotic lesions in the eyegrounds and in the myocardium with reversal of T waves as well as reduction in size of the cardiac configuration by x-ray. Even when there was no significant change in blood pressure levels these changes in eyegrounds and myocardium often took place with an improvement in the general condition of the patient. The author feels that the outlook for arteriosclerotic cardiovascular disease and renal pathology has been entirely altered by the results of the rice diet as he has observed them.

Electron Microscope in Relation to the Medical Sciences: Stuart Mudd, Professor of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia—By means of this microscope, which magnifies from .002 microns, not only can the finer structure of bacteria be visualized, but the structure of bacteriophages and viruses can be seen. Also the submicroscopic elements of tissue can be seen, as sections may be made of tissues so thin that details of structure never before visible can be easily studied: for ex-

ample, the chromosomes of nuclei as well as the variations in the striation of muscle. Photographs were shown of bacteria being attacked by phages and it was pointed out that phages utilize the protoplasm of the bacteria to synthesize new phages instead of reproducing by fission as do bacteria. It was suggested that alteration of this kind might suggest a lead for the microbic origin of cancer, since the metabolism of the cell could be altered by such synthesis of new material. Many fields of research will be opened by the new approach of the electron microscope.

PRESENT STATUS OF AUREOMYCIN THERAPY: Maxwell Finland, Associate Professor of Medicine, Harvard Medical School, Boston, Mass.—Oral administration is the most satisfactory, although the intravenous method may be used, but the material is too irritating to tissues for intramuscular injection. So far no untoward effects have been found in either animals or man. A single dose is excreted in the urine over a 24-hour period. It acts on a wide range of bacteria, proteus and pyocyaneous being most resistant. Of special value is its effects on rickettsial diseases and viral infections. In such diseases as Rocky Mountain spotted fever, murine or epidemic typhus, scrub typhus, Q-fever, and Brill's disease, improvement is seen within 24 hours, the temperature drops before the third day, and the rash fades. These effects occur without respect to the time of the disease; late cases respond as well as early ones. Excellent results are obtained in lymphogranuloma venereum, especially in acute cases, as well as in atypical pneumonia, of which three series of cases have been reported. Bacterial pneumonias also respond to aureomycin, the action being comparable to penicillin. Staphylococcal infections of the lungs, as well as more superficial infections as of the skin in pyoderma, clear readily, as do many cases of osteomyelitis. The effect on Salmonella infections is not so dramatic, only about 50 percent responding. In typhoid fever, chloromycetin is much more efficacious. Bacilluria has improved where other methods have failed, though infections with proteus and pyocyaneous have proved stubborn. In these instances sometimes streptomycin and aureomycin given together have overcome this type of infection. The results in brucellosis are not as yet determined; some relapses have occurred in melitensis and occasionally in abortus. However, in these diseases the results are better than one would expect by laboratory findings. General peritonitis due to perforated ulcer (a case of typhoid was cited) has been cured. It is useful in preparing the abdomen for peritoneal lavage as in treating total anuria and in preparation for operations on the bowel. It is being used as a borate salt in conjunctivitis, corneal ulcers, and other pyogenic infections of the eye. It is not successful in vernal catarrh, although it is for dendritic conjunctivitis. It has proved successful in malignant pemphigus and in herpes zoster, especially when it affects the eye. In acute gonorrhea it is as effective but no better than penicillin and must be given in the dose of 2.5 gm. orally over a 20 to 36-hour period. It will cure granuloma inguinale and primary syphilis, but is less striking than penicillin in the latter condition. Dosage consists of 1 gm. every 4 to 6 hours, with reduction to 0.5 gm. every 6 hours after improvement sets in; or by intravenous injections of 500 mg. in 5 percent dextrose given over an hour. Intramuscular administration is too painful. Side effects are nausea, vomiting, and diarrhea; these have developed since the product has been made on a large scale and may be due to impurities. These side effects may be minimized by giving the aureomycin with food, alkalies, or chloretone, and may subside while treatment is continued. No damage to blood or liver has been reported and there are no central nervous system effects.

CHLOROMYCETIN AND AUREOMYCIN: THERAPEUTIC RESULTS: Theodore Woodward, Associate Professor of Medicine, University of Maryland School of Medicine, Baltimore—These antibiotics are effective over a wide range of bacteria both gram-positive and gram-negative, but their striking property lies in their effect upon the rickettsial and some of the virus diseases. A dose of chloromycetin is widely disseminated in the body and one-half the blood level appears in body fluids such as in bile and breast milk. In typhoid fever, brucellosis, and tularemia it has proved highly effective even when blood cultures were positive before treatment was started. In 21 cases of typhoid treated in Malaya only four relapses occurred and these were readily controlled. The average duration of fever after medication was started was only three and one-half days. There were no deaths. The experience of this author was that both aureomycin and chloromycetin were effective in acute brucellosis, but that relapses occurred. In tularemia aureomycin was more effective than chloromycetin and even an extremely ill patient recovered in 16 days, the temperature dropping within 24 hours. In a large series, however, the average duration of fever after treatment was 2½ days. Both antibiotics were equally good in the treatment of rickettsial diseases as

previously stated. However, in the virus diseases such as lymphogranuloma venereum, psittacosis, and virus pneumonia, aureomycin seemed to give superior results.

POLIOMYELITIS: EARLY DIAGNOSIS AND EARLY MANAGEMENT OF ACUTE CASES: John R. Paul, Professor of Preventive Medicine, Yale University School of Medicine, New Haven, Conn.—The importance of early diagnosis during the prodromal stage was stressed, for after paralysis develops the virus infection is probably over. Since the earlier epidemics of 1907 and later, there have been changes in the clinical picture in this country as well as on the continent and in England, the disease occurring more often in adults than previously; in 1907 only 10 percent were over 15 years of age; in 1946, 25 percent. Since 1916 the non-paralytic cases have increased from an estimated 16 percent to 70 percent, but in the early stage there is no way of telling which will develop paralysis. During the incubation period of the disease any emotional or physical trauma or over-exertion is likely to precipitate symptoms of paralysis and, therefore, bed rest should be insisted upon. Pain is an early predominant feature more frequently in the adult than in the child, the pain simulating strain of the back or legs. There is also a low grade fever; later the temperature may rise to 101° F.; the neck becomes stiff, difficulty in voiding occurs, and abnormal reflexes develop. In the early stage no overt diagnosis may be necessary to control the patient nor is it necessary to send him to the hospital. Cooperation of the family must be secured. Lumbar puncture is not necessary, for in the early stage it is negative and later it is always positive. Paresthesias, restlessness, sensory changes, and deep pain in the legs and back are irritation phenomena; changes in deep reflexes and especially in the abdominal reflexes give a hint of the condition. Any hospital should accept these patients when hospitalization is necessary with the development of frank disease, for "common sense" isolation is all that is necessary. There is no specific therapy; strong analgesics should be avoided as masking the picture and not relieving the pain; moist packs while essential should not dominate the whole picture; shell casts only should be used; care of the airways should be meticulously observed with postural drainage and even tracheotomy if necessary. Bladder paralysis is common in the adult, but an indwelling catheter should not be used for long periods.

THE USE OF ISOTOPES AS METABOLIC TRACERS: Dewitt Stetten, Chief, Division of Nutrition and Physiology, The Public Health Research Institute of the City of New York, Incorporated, New York, N. Y.—Isotopes of the various elements are of great value as tools to investigate action of biochemical compounds in the body, for they act in every respect like the parent compound. Not only can the synthesis of various substances be accurately followed through their intermediate stages, but the rate of tissue formation can be determined. For instance, although the depot of fat remains constant it was shown that the half life of the isotope in this fat in mice was 5 to 6 days and in the rat 9 days, even though the weight at the end of the experiment remained constant, demonstrating that half the fat had been replaced by newly synthesized tissue. The rate of glycogen formation in the liver has been similarly determined, and since the isotope passes through the placenta barrier it has been possible to show that the fetus makes and destroys more glycogen than its parent. In diabetes it has been demonstrated that there is an inhibition in the synthesis of fatty acid, increased by insulin, which fits into the theory of the action of insulin and accounts for the gain in fat depots with the use of insulin in both diabetic and normal subjects. By the use of radiant energy, therefore, studies can be made of (1) anatomical distributions of substances; (2) rate of turn-over; (3) precursors of vital substances; and (4) the corollary changes in normal reaction rates under abnormal circumstances; in fact, light can be thrown on much intermediate metabolism throughout the body.

THERAPEUTIC CONSIDERATIONS IN ULCERATIVE COLITIS: Walter L. Palmer, Professor of Medicine, University of Chicago School of Medicine, Chicago, Ill.—Bargen has differentiated the types of ulcerative colitis and called the idiopathic form thrombo-ulcerative colitis. No etiological organisms have been generally recognized by most observers, although there is undoubtedly an inflammatory situation present. Remissions and exacerbations are often governed by psychogenic factors. By proctoscopic examination, 95 percent of cases show extensive ulceration in the rectum and sigmoid and the proctoscopic picture is more diagnostic than the x-ray. Differential diagnosis includes the well-known causes of inflammatory disease of the bowel. Treatment consists of: (1) rest in bed until the diarrhea ceases; (2) diet of high protein, high calorie, low residue with high vitamin content (parenteral feeding may be necessary); (3) medical ileostomy (Machella-Miller type) with formula feedings in severe cases; (4)

blood transfusions and vitamin K, antispasmodic drugs, sedatives, and opiates as indicated. The value of chemotherapy is debatable and, although the stool may present cultures of gram-positive organisms, sulfaguanadine will transform the flora to gram-negative types. These in turn may be largely eliminated by streptomycin. However, this does not alter the course of the disease. Psychotherapy is of great value in many cases whether through the sympathetic attitude of the attending physician or through psychoanalysis. The cost of this illness is very great, for remissions requiring hospitalization are frequent. Occupational therapy should be encouraged for the long bouts of hospital confinement.

MALIGNANT TUMORS OF THE AMPULLARY AREA AND PANCREAS: Allen O. Whipple, Clinical Director of Surgery, Memorial Hospital, New York, N. Y.—This is the concern of the internist, as well as of the surgeon, for the outlook for cure of these conditions rests in early diagnosis. In spite of the extensive radical surgery necessary in these cases, the operative mortality in a series of 59 patients was only 13.6 percent, and 30 percent lived 3 years or more. In all, there are 220 cases operated on by the technique outlined, reported from all large centers in the United States and Canada.

THE TREATMENT OF BLEEDING ESOPHAGEAL VARICES BY PORTACAVAL SHUNTS: Robert R. Linton, Assistant Clinical Professor of Surgery, Harvard Medical School, Boston, Mass.—In a series of 108 cases of cirrhosis and of Banti's disease in which bleeding varices had developed, only 37 percent of the patients were alive in 1 year. Such varices may develop from intrahepatic disease, as in portal cirrhosis, as a result of thrombosis of the hepatic veins, or as the result of extrahepatic circulatory congestion and portal hypertension as in Banti's disease. Anastomosis of the portal vein and the vena cava is done through direct anastamosis or indirectly by means of the splenic or renal or even the adrenal vein. By these shunts not all blood by-passes the liver and the intravascular pressure in the varices is relieved. In the majority of cases hemorrhage did not reappear. In the few in which it did, the loss of blood was not exsanguinating.

THE USE OF MIXTURES OF PROTAMINE ZINC AND REGULAR INSULIN: Randall G. Sprague, Assistant Professor of Medicine, University of Minnesota (Mayo Foundation), Rochester, Minn.—In order to control postprandial hyperglycemia and glycosuria and at the same time avoid nocturnal hypoglycemic reactions, a mixture of free insulin and protamine zinc insulin is used in many cases of diabetes. Although many patients with diabetes do not require any insulin, others are not controlled by protamine zinc alone. A mixture of 2:1 or 3:1 can be given by the patient in the morning, and if necessary a dose of free insulin later in the day; it is not difficult to instruct the patient in this technique, and it is necessary if maximum control of laboratory findings is considered essential. It is possible that globin insulin or the new preparation N.P.H. 5 will obviate the necessity for these mixtures.

THE ALLERGY FACTOR IN DISEASE: Robert A. Cooke, Director of Department of Allergy, Roosevelt Hospital, New York, N. Y.—There is undoubtedly an allergic factor in many diseases of unknown origin, as well as in diseases definitely known to have allergic components, such as tuberculosis (tuberculin test), pneumonia (reaction to specific polysaccharides), certain fungous and parasitic diseases, diphtheria, and tetanus. Allergy offers a new angle of approach in such diseases as periarteritis nodosa and other collagen diseases. As regards asthma, urticaria, vasomotor rhinitis, etc., bacteria play an important part especially in the early phases of these diseases and should be approached from a surgical standpoint to secure complete eradication of the focus, usually in the upper respiratory tract. Especially is bacterial allergy a predisposing factor to asthma in the older age group. Drug allergy is often difficult to recognize, but is especially important since the advent of the antibiotics and sulfonamides. The criteria should consist of: (1) adequate contact; (2) symptoms of typical allergy; (3) eosinophilia; (4) positive transfer tests (although these can seldom be obtained in drug allergy); and (5) some weight should be given to a family history of allergy. All drugs are potential allergens, but sensitization is developed more easily through the skin than by the oral administration. *Histamine antagonists:* It is commonly agreed that histamine is released in the sensitized cell, especially in the whealing type of reaction, as in urticaria, hay fever, and vasomotor rhinitis. There are 18 to 20 drugs available on the market which are antagonists to histamine and all are varyingly effective and with individual side effects of more or less importance. Their benefit is palliative only and is less in dermatitis and asthma than in the types of allergic conditions mentioned. They are a useful adjunct but cannot supplant hyposensitization in the allergic individual, except in very mild cases.

THE RESPONSE OF THE ADRENAL CORTEX TO DISEASE AND INJURY: J. S. L. Brown, Professor of Medicine, McGill University Faculty of Medicine, Montreal, Canada—The development of our conception of diseases, such as Addison's, Cushing's, etc., consisted first of a description of clinical symptoms, next of the chemical modifications which occur during the disease in tissues, blood, and urine, and lastly, of a study of the hormones themselves, which has been possible during the last 10 or 12 years. Three different types of hormones are recognized: (1) desoxycorticosterone which controls the electrolytes and water metabolism; (2) the glucocorticoids which have to do with the mobilizing and converting of protein to carbohydrate; and (3) androgens and, to a less extent also, estrogens and progesterone. Each of these may act separately or there may be overactivity of all which accounts for the protean manifestations of Cushing's syndrome in which too there may be relative predominance of one or more of the hormones. Selye has shown the interdependence of all of the endocrines in the alarm reaction, and it is possible by laboratory methods to determine quantitative values for the glucocorticoid hormones under conditions of disease or trauma. In acute insults these values always rise but in chronic conditions they usually remain at a normal level. Reasons for this phenomenon are given. In Cushing's syndrome the values are also raised and Albright suggested the use of testosterone to oppose them and to aid in nitrogen retention. With this medication, the "diabetic" curve of blood sugar also returned to normal. Cushing's disease may be artificially produced by the injection of the adrenotropic hormone now on the market, resulting in an increase in 17 keto steroids, a rise in the glucocorticoids, sodium retention, edema, and an altered sugar tolerance. There is also antigenic action, characterized by reduction of lymphocytes, a leucocytosis, and an outflow of eosinophiles. The teleological explanation for the adrenal cortical response to trauma or disease would appear to be to counteract the threat of starvation by mobilizing protein for transportation to the liver and to make carbohydrate available for energy purposes; in pregnancy, to provide for a rapid transfer of foods from mother to fetus; in injury, to provide building blocks for repair of tissue. In chronic disease it would appear that all the tissues of the body compete for nitrogen and so the body goes into positive nitrogen balance. The rationale for such effects as are produced by non-specific protein injections to stimulate increased productions of pituitary hormones by creating an acute insult to the body is thus explained.

GOUTY ARTHRITIS: John H. Talbott, Professor of Medicine, University of Buffalo School of Medicine, Buffalo, N. Y.—This disease is characterized by a faulty uric acid metabolism and values are usually found to be abnormal not only in the patient, but in others of the family in whom no symptoms exist. Sex incidence is about 95 percent in the male; the diagnosis should be regarded with suspicion in the female. Age incidence is chiefly in middle age, but the disease has occurred in the seventh or eighth decades and in a child of 6 years. The typical acute attack is associated with fever, local swelling, leucocytosis, and a red, hot joint. However, many attacks are not typical. The disease may attack any joint or combination, although the most often affected is the metatarsophalangeal joint of the big toe. The x-ray picture shows a typical punched out appearance when positive, but it usually does not become positive for many years. The laboratory confirmation of the disease depends upon the high uric acid values in the blood, but this laboratory determination is not easily done and is often not dependable. A single laboratory technician should be assigned the task of doing these tests in order to insure accuracy. The upper limit of normal for uric acid is about 6 mg. percent. In a series of 500 controls only four had values above this reading. The average elevation in the gouty series was 8.8 mg. percent. Treatment of the acute stage calls for bed rest, an increased fluid intake, analgesics, and colchicine, the specific drug. Colchicine is given, one tablet (0.5 grams) every hour, or two tablets every 2 hours, for 10 to 12 tablets, or until gastro-intestinal symptoms arise, when the medication should be stopped and paregoric given. As many as three courses of the drug may be necessary. For the chronic stage, or between attacks, restriction of purine foods should be observed with a liberal fluid intake and colchicine. Several pills a week or one or two a month may serve to prevent or lessen the incidence of attacks. When deforming uric acid deposits develop, becoming large and breaking down to cause sinuses, surgical excision should be done.

MIGRAINE AND HISTAMINE CEPHALALGIA: Bayard T. Horton, Associate Professor of Medicine, University of Minnesota (Mayo Foundation), Rochester, Minn.— Dr. Horton first described the latter syndrome in the same auditorium in which he spoke, ten years previously. Moving pictures in color were shown of patients having spontaneously developed an attack of histamine cephalal-

gia, and others in whom the attack was induced by the injection of 0.25 mg. of histamine. The syndrome lends itself very well to this mode of presentation; the temporal arteries are seen to swell, the eye to water profusely, and the conjunctiva to become engorged; beads of perspiration form and stand out on only one side of the forehead and the affected side of the face becomes flushed with marked rhinorrhea and a mucous discharge from the one nostril while the other remains unaffected, a most striking picture and one not easily forgotten. Intravenous dihydroxy-ergotamine is a specific cure for the attack and is effective within a few seconds. This type of headache always occurs on the same side of the head and is characterized by its extreme severity. Cases were presented in which the condition had not been recognized and the patient had had ganglionic resections, even ligation of the carotid artery in an effort to control the pain. The tendency to have this type of headache is much reduced by histamine desensitization, but relief is usually not permanent and later courses may have to be given.

Dr. Horton stressed the necessity for re-education of the migraine patient, to reduce nervous tension, and described the personal reaction patterns of the migraine subject. He outlined the various stages of a typical migraine attack. The intracranial stage is not relieved by ergotamine, but the second, extra-cranial stage, is relieved by D.H.E.—most effectively by intravenous injection or by gynergen subcutaneously. No known procedure will prevent the attacks, but the patient sometimes can abort them by an oral combination of ergotamine tartrate and caffeine. Patients may be taught to give themselves injections in order to terminate the acute attack. However, a consistent effort should be made to re-educate the patient, in order to reduce nervous tension.

THE ETIOLOGY OF RHEUMATIC FEVER: Homer F. Swift, Member Emeritus of the Rockefeller Institute for Medical Research, New York, N. Y.—Although it is often stated that the cause of rheumatic heart disease is unknown, much evidence leads to the conclusion that the essential features in its etiology are now understood. In all cases of rheumatic fever that have been studied, it has been shown that from 10 days to 3 weeks preceding the attack the patient has had an infection caused by one of the A Group of streptococci. Until Lancefield, of the Rockefeller Institute, and Griffin, of England, classified and studied the entire field of streptococci and isolated and described the "A Group" which are the pathogens in human disease, this knowledge was impossible to obtain. This A Group comprises 5 percent of all streptococci that are found in human subjects. The clinical picture of rheumatic fever has been changing, so that now one rarely sees the fulminating polyarthritis, and many cases of rheumatic heart disease may develop without the arthritis component. If a patient is examined for streptococci at the onset of the attack, no organism of the A Group is found, but serologic tests reveal the presence of antistreptolysin or of streptokinase, and 99 percent of patients show these immune substances. But the manifestations of rheumatic fever, as in allergic diseases, depends upon the individual susceptibility, more "on the soil than on the seed." Dr. Swift presented experiments on rabbits to demonstrate the development of sensitivity by repeated injections of various strains of Group A streptococci over a prolonged period of time and demonstrated that where they were hyporeactive to the types injected they were hyperreactive to other strains of Group A. This course of events undoubtedly occurs in individuals subject to streptococcus infections, especially of the respiratory tract, tonsils, etc., the susceptible individual becoming sensitized by some types of streptococci in the A Group and so hyperreacting to others of the group when exposed. The experimental animals showed typical Aschoff bodies in their myocardial structures and the formation of typical lesions on the endocardium.

HYPERSPLENISM: Charles A. Doan, Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio—This condition is divided into primary and secondary hypersplenism. The mechanism of many blood diseases, notably congenital hemolytic icterus and thrombocytopenic purpura, was described. The evidence for hypersequestration of cells in the unique vascular system and sinuses was outlined, with the loss of potassium from such cells and subsequent injury and destruction. Criteria for splenectomy were given, with special emphasis on the study of the bone marrow to exclude such conditions as myelophthisis or similar aplastic disease where the spleen is acting in its extramedullary capacity of hematopoiesis, or where primary defects of the bone marrow can be demonstrated. When splenectomy is decided upon, great care should be exerted in searching for accessory spleens; as many as 10 have been reported, largely located in folds of the mesentery. These often account for recurrences of the blood dyscrasias.

—Reported by
L. MARY MOENCH, M.D., F.A.C.P.

World Health Organization

ACTIVITIES 1949

Background

The World Health Organization, which officially became a specialized agency of the United Nations on September 1, 1948, following two years of work by an Interim Commission, is helping its member governments raise health standards through field demonstrations, advisory services, fellowship, a worldwide disease-warning service, study by expert committees, research, and emergency aid in epidemics.

In its Constitution, called the "Magna Charta of Health," WHO declares that health is not merely the absence of disease or infirmity but "a state of complete physical, mental, and social well-being." Working toward this goal, WHO is conducting top-priority programs in six fields: malaria, tuberculosis, venereal disease, sanitation, maternal and child health, and nutrition.

High-Priority Programs, 1949

1. *Malaria:* This disease strikes an estimated 300,000,000 each year; of these, 2 to 3,000,000 die; others are weakened so much that their productivity as workers is greatly reduced. In August, 1949, seven WHO demonstration teams were fighting malaria in Afghanistan, India, Pakistan and Thailand, six of them in co-operation with the UN Children's Fund, which provides DDT-spraying supplies in areas where malaria is a special foe of children.

Malaria control projects were launched in April, 1949, in Hungary, Rumania, Yugoslavia, and Bulgaria with the aid of two WHO experts and with supplies provided by the Children's Fund. In the same month, two WHO experts were lent to Iran and another reached India to lead an attack on the "foothills malaria" that has caused the fertile Terai region of the Himalayas to be abandoned.

In May, 1949, WHO sent a public health engineer to Turkey with samples of the latest DDT preparations for use in anti-malaria campaigns.

In Greece, where WHO has aided in malaria control, 4,733 communities and 702,705 acres of land had been sprayed with DDT by the end of 1948. In some areas, the malaria rate was cut from 80 percent of the population to 5 percent; as a result, food production increased in some districts as much as 70 percent. Before malaria control, the average gross income of families in certain localities was $196; after malaria control, income rose to $358.

Dramatic results of malaria campaigns in which WHO participated were also reported by Italy and Sardinia in early 1949. Italy, which normally has had thousands of deaths caused by malaria, reported a record of only four such deaths in 1948.

Through the Red Cross and Red Crescent Societies, WHO gave help in 1948 in controlling epidemic malaria in the Tulcea region of Rumania.

In a new five-year program planned by WHO and the Food and Agriculture Organization, at least 10,000,000 acres of agricultural land inadequately worked by disease-ridden people will be developed. WHO and FAO will seek to increase food production in six areas by combating diseases, particularly malaria, and simultaneously by applying new techniques for soil improvement.

2. *Tuberculosis:* An estimated 50,000,000 suffer from tuberculosis each year; 5,000,000 die.

WHO is co-operating (with the UN Children's Fund, the Danish Red Cross and its Scandinavian associates) in the International Tuberculosis Campaign which was started in Europe in 1948 and is being extended this year to the Near East, the Far East, and the Western Hemisphere. In this campaign, it is expected that 100,000,000 children will be tested for tuberculosis; those found free of infection will be inoculated with BCG (Bacillus Calmette-Guerin) vaccine at a cost of 10 cents per child. By August, 1949, some 17,500,000 had been tested and 8,000,000 vaccinated.

As fast as children are tested and vaccinated in the Campaign, record cards are made available to WHO for the first large-scale research on effectiveness of BCG vaccine. Through statistical analysis of millions of records, WHO hopes to find solutions to questions long unanswered about tuberculosis.

A C-47 airplane, loaned to the International Tuberculosis Campaign by the United States Air Forces, regularly flies drugs and medical supplies from campaign headquarters in Copenhagen to Eastern European countries being aided by WHO and the Children's Fund. Streptomycin is provided

for use against certain types of tuberculosis. (The same plane carries penicillin for use in venereal disease campaigns in which WHO and the Children's Fund are assisting.)

A survey of the tuberculosis problem in the Middle East was made by WHO in April and May, 1949, when an expert toured Iran, Iraq, Saudi Arabia, Syria, Lebanon, Jordan, Cyprus, and Aden. A similar survey has been started in Latin America.

To help the Egyptian Government find out how much tuberculosis is present, a WHO technician went to Cairo in April, 1949, to demonstrate x-ray testing techniques and prepare the way for a mass x-ray campaign.

In China, a chain of tuberculosis centers has been established by WHO in Shanghai, Peiping, Tientsin, Nanking, Taiwan (Formosa), and Canton. The Canton center, in its first month of operation, gave free diagnoses to 2,000 persons. Treatment is also given free, if necessary. In addition, WHO has arranged with the Chinese Government to send three doctors to Europe for study; a WHO specialist has given courses in x-ray technique; a new National Tuberculosis Association has been established; and 10 sets of x-ray apparatus have been put into use.

With the approval of the Polish Government, WHO has set up a plan for tuberculosis control in Poland, has made available x-ray services, has inspected and repaired equipment supplied by UNRRA, has trained more than 100 technical assistants in care and operation of x-ray equipment, and has published in the Polish language a handbook on practical x-ray technique.

In Greece, WHO's staff assisted in the opening of a modern chest hospital in Athens and in the establishment of mass x-ray centers in several cities. By the end of 1948 an estimated 250,000 people in Greece had received x-ray examinations.

WHO experts made technical visits in 1948 to Czechoslovakia, Egypt, France, Italy, and North Africa; advised Ceylon authorities about a comprehensive anti-tuberculosis program; investigated Ethiopia's tuberculosis problem; and conferred with Italian authorities about a five-year tuberculosis control program calling for equipment for 152 tuberculosis dispensaries, including 12,595 beds.

A WHO team was sent to India in the summer of 1948 to set up a laboratory near Madras for the manufacture of BCG vaccine used for immunization against tuberculosis.

3. *Venereal diseases:* WHO is seeking to reduce, through modern treatment, the high postwar rate of venereal infections. An estimated 2,000,000 deaths yearly are attributed to syphilis alone. Venereal disease affects up to 50 percent of the population in parts of eastern Africa, 12 percent in India's Province of Madras, 32 percent in northeastern provinces of China. Syphilis costs the United States some $100,000,000 per year in man-days lost in industry. War and occupation increased venereal disease far above normal rates in Eastern Europe—in Warsaw, 12 times the pre-war rate.

One of WHO's most extensive projects has been to combat, in collaboration with the UN Children's Fund, prenatal and infantile syphilis with penicillin in countries where governments are conducting mass venereal disease campaigns. Such programs have been started in Bulgaria, Finland, Italy, Hungary, and Yugoslavia.

Newest techniques of using penicillin against venereal disease were demonstrated by a WHO consultant in Czechoslovakia, Hungary, Bulgaria, Yugoslavia, and Italy in the spring of 1949. In some villages of the Bosnian Hills, Yugoslavia, he found that as many as 50 percent of the children showed secondary syphilis lesions.

WHO started a venereal disease control demonstration in India in April, 1949. An American doctor and nurse and a Norwegian serologist demonstrated penicillin treatment to Indian doctors and nurses. WHO-UNICEF campaigns against venereal disease are planned in India, Burma, Siam and Pakistan.

An on-the-spot survey of venereal disease in Rhine River ports was conducted by experts from five countries under WHO auspices in August, 1949. International action to control this disease along the river is called essential because of the volume of travel from port to port; in Rotterdam, 49 percent of the cases diagnosed in 1947 originated in other countries.

To study newest methods of venereal disease control, a group of specialists from Europe, Latin America, and Asia was brought to the United States in August, 1949, by WHO and the U.S. Public Health Service.

Poland, in consultation with WHO, was the first country in Europe to launch a national anti-syphilis campaign based on penicillin treatment. Between April and September, 1948, more than half a million persons were examined and more than 43,000 cases of syphilis treated.

A comprehensive program for venereal disease control was proposed to the Ethiopian Government,

and advice was given to the Philippine Government by a WHO consultant who went to Manila in late 1948.

In Naples, with supplies provided by the Children's Fund, a pilot demonstration in treatment of children and pregnant women was conducted in 1948, and the Italian Government has requested that similar demonstrations be given in other Italian cities.

4. *Environmental sanitation:* More than three-quarters of the world's population are still the victims of diseases resulting from poor sewage disposal, unsafe water supplies, insects, and inadequate protection of milk and food.

To combat disease-carrying insects in Middle East refugee camps, WHO and the UN Children's Fund launched a sanitation program in the spring of 1949. It includes DDT spraying against malaria-carrying mosquitoes; use of DDT and gammexane against flies, which cause severe intestinal diseases and eye infections among Palestine refugees; construction of latrines, burying of refuse, and other public health measures.

WHO has also given practical field aid in sanitation projects in Ethiopia, Greece, and China in recent months. In Ethiopia, DDT has been used against flies and lice, city dumps have been cleaned up, and one uninhabitable area has been converted into a city square. In Greece, DDT has been directed against flies, bedbugs, lice and fleas. A WHO sanitary engineer has assisted Chinese officials in improving city water supplies and city sewage disposal systems.

A $1,000,000 attack on poor sanitation, basic cause of filth-borne, insect-carried and water-transmitted diseases, has been planned by WHO for 1950. The program calls for 15 demonstration teams in various areas, health projects in rural districts, and international training courses in three regions.

5. *Maternal and child health:* Three babies out of every 10 born alive die in infancy in many parts of the world today. Yet with improved health services, the death rate has been cut in some areas from 30 per 100 births to 3 per 100 births in a comparatively short time. WHO has formed the Expert Committee on Maternal and Child Health, which will study the problem on an international scale, and has offered fellowships, demonstration teams, and other aid to members.

6. *Nutrition:* WHO and FAO are co-operating in a "food for health" program which includes stress on health education of the public. The agencies hope to break the vicious circle of insufficient food, which causes poor health, and poor health, which in turn makes a population too weak to produce the food it needs.

Other Activities

Mental Health: Studies in some countries have shown that neuroses cause more absenteeism from work than the common cold and that as many as one-third of all British army discharges were due to mental disorders. To find some of the answers to mental health problems, WHO will concentrate at first on gathering information about mental health in rural communities, in industrial units, and among university students. The program will receive increased emphasis in 1950.

Cholera: As a first step toward complete eradication of cholera, which experts say is possible but which has never been attempted on an international basis, WHO will send two demonstration teams to Bengal in 1950. The teams will work in two districts, one in India and one in Pakistan, where cholera is continuously present.

An epidemic-watchdog service is operated by WHO through world-wide broadcasting facilities. Ten powerful transmitters near Geneva, beaming radio reports to every continent, broadcast twice daily the latest official information on epidemic diseases and quarantine measures. A WHO Epidemiological Intelligence Station at Singapore provides special service for the Pacific and Indian Ocean areas.

Medical training: WHO has awarded more than 500 fellowships to help doctors and public health personnel, isolated by the war from scientific advances, obtain up-to-date training. Eighty fellowships in the special field of maternal and child health were made available in 1949. Medical literature was supplied to 13 countries in 1948 and 1947.

Training of medical and nursing personnel has also been provided by field missions. In the remote mountains of western China, a WHO Mission has trained students in basic medical and surgical techniques, prepared an illustrated manual on surgery, produced smallpox vaccine and even made peg legs for cripples.

Inoculation and vaccination certificates for travelers are supplied by WHO. The certificates provide internationally standard forms for records of inoculation and vaccination against smallpox, yellow fever, typhus fever, and other diseases.

Emergency Aid

In addition to its normal work of helping governments through demonstrations and consultations, WHO takes direct action when emergencies strike.

Elizabeth Blackwell

THE WOMAN OF THE CENTURY

Bertha Van Hoosen, M.D.

ONE HUNDRED YEARS AGO gainful occupations for women were limited to housework, handwork, and teaching, and were in the lower brackets as to wages and requirements for skill and education. So little attention was paid to the education of girls in the nineteenth century that Boston, hub of culture, did not have a high school for girls until 1826, and because of determined opposition it was closed in 1828 and not reopened until the 50's.

Into this narrow, restricted woman's world Elizabeth Blackwell was born February 3, 1821. That she chose a medical career and succeeded in becoming the first woman M.D. in the modern meaning of that term seems, in retrospect, nothing short of a miracle and invites study into the essential and determining factors of her life.

What creative power lay behind these pioneer firstlings? Was it the presence of crowds behind, pushing them to the front, or was it quite the contrary—the result of so little, practically no, competition?

As a physician and one interested for many years in genetics, I look upon Elizabeth Blackwell's accomplishments as a manifestation in the growth of an extraordinary pattern of chromosomes that were unusual as to kind and number. I believe a similar chromosomic mystery accounts for but one Shakespeare, one Edison, one Marie Curie, and many centuries may elapse before the patterns are duplicated.

The red calf born in our pure breed herd of Holstein Fresian, black and white cattle, when an attempt was made to introduce a strain of another pure breed Holstein Fresian herd remarkable for type and performance, shows that the Mendelian law carries back through pedigree and history farther than we are able to trace.

The Elizabeth Blackwell Memorial address presented before a meeting of the Medical Women's International Association, Copenhagen, Denmark, July 13, 1949.

After reading Elizabeth Blackwell's *Pioneer Work in Opening the Medical Profession to Women*, I have listed eighteen qualities (I think of them in terms of chromosomes) that seem to have a large and definite place in her make-up. These qualities are Persistence, Culture and Sense of Humor, Physique, Motive, Self-Reliance, Spirituality, Patience, Courage, Humility, Industry, Honesty, Loyalty, Fearlessness, Personality, Creative Power and Intuition, Leadership, Teaching, and Writing. Many of these qualities are so interwoven that they strengthen and aid each other in every performance.

Elizabeth Blackwell's English nationality accounts for her persistence, a going-on resolutely in spite of opposition, importunity, or warning.

Another happy quality to guarantee success was culture, that enlightenment and refinement of taste acquired by the individual's intellectual and esthetic training, as well as the way of life of a group. Elizabeth Blackwell's memoirs mention that it was a family custom for the children to make requests of their parents in poetic form and to receive the reply in verse. The atmosphere of the Blackwell home was cultured, and this culture was lightened by a sense of humor, a characteristic of all the members of the Blackwell family, but especially of Elizabeth.

Perhaps no career makes greater demands upon physical strength than medicine. Elizabeth Blackwell was blessed with a perfect physique. Her muscles were corded steel, her delicate hands had a grip of iron. She would pick up the other children and carry them about the house till, tired out with laughter and struggling, they consented

to her terms of release. While still in the school room her feats of strength were astonishing.

If there are master motives that move and guide the pioneer, we can find them in Elizabeth Blackwell. Strangely enough, this woman who was to stand as a beacon to the distaff side of medicine early in life had no sympathy or patience for the ill or the ailing. When she was calling on a family friend who was dying of a malignant disease, the friend said to her that if she, Elizabeth, had studied medicine, it might have saved her life. "I would have gone to you before it was too late. Why do you not study medicine, Elizabeth?" It sickened Elizabeth. The very thought of blood was repulsive to her. Nevertheless, she could not rid her mind of the idea. Perhaps this was, after all, what she was looking for. No woman had ever done it! She could, if it could be done. She would become a physician!

Determined now to study medicine, there seemed to be no one who could or would give her the necessary financial assistance. The friend who had promised to see her through told her that she could help only to the extent of a one hundred dollar loan. At once she saw that she must depend upon herself, and as teaching was her only resource, she accepted a position to teach music in a school in Asheville, North Carolina. This school belonged to Rev. Mr. Dickson, who had been a physician and could become her preceptor, for those were the times when medical students spent two or three years studying with a practicing physician before entering medical school.

Of this journey to Asheville her memoirs record: "This was before the time of railroads; the roads through Kentucky were little traveled; several rivers had to be forded, and three lines of mountains to be crossed. Two of my brothers determined to drive me to my unknown destination. So the carriage was packed with books and comforts for the eleven days' journey, and I left home for Asheville, North Carolina, to begin preparations for my unknown career.

"We at last reached our destination—viz., the school and parsonage of the Rev. John Dickson, formerly a physician, where I was to teach music.

"I had been kindly welcomed to my strange new home, but the shadow of parting with the last links to the old life was upon me. The time of parting came. My two brothers were to leave on their return journey early the following morning. Very sadly at night we had said farewell. I

ELIZABETH BLACKWELL, M.D.

retired to my bedroom and gazed from the open window long and mournfully at the dim mountain outlines visible in the starlight—mountains which seemed to shut me away hopelessly from all I cared for. Doubt and dread of what might be before me gathered in my mind. I was overwhelmed with sudden terror of what I was undertaking. In an agony of despair, I cried out, "Oh God, help me, support me! Lord Jesus, guide, enlighten me!' My very being went out in this yearning cry for Divine help. Suddenly, overwhelmingly, an answer came. A glorious presence, as of brilliant light, flooded my soul. There was nothing visible to the physical sense; but a spiritual influence so joyful, gentle, but powerful, surrounded me that the despair which had overwhelmed me vanished. All doubt as to the future, all hesitation as to the rightfulness of my purpose, left me, and never in after-life returned. I knew that, however insignificant my individual effort might be, it was in a right direction and in accordance with the great providential ordering of our race's progress.

"This is the most direct personal communication from the Unseen that I have ever consciously

had; but to me it is a revealed experience of Truth, a direct vision of the great reality of spiritual existence, as irresistible as it is incommunicable."

After teaching for two years in the South, she went to Philadelphia, then the medical center of the United States, and hoped to find there a medical school where she could begin studying medicine. Fortunately, she boarded with the family of Dr. William Elder (author of the life of Dr. Kane, the Artic voyager). One by one the medical schools in Philadelphia turned down her application, as did the medical schools in New York City. In desperation, she applied to twelve of the most promising small medical schools throughout the country. Not one of them answered, and as time for the winter session was approaching rapidly, anxiety was a great strain on her patience. Finally a letter came from the medical department of Geneva University in New York, stating that her application had been accepted, and disclosing that the question of admitting a woman had been turned over to the student body and had been decided in the affirmative. The influence of a letter from Dr. Elder to the president may have been an unestimated factor. How many young women would have had such patience, such calm, such endurance, such self-possession?

Every step of her precarious way, from the moment that she entered medical classes filled with high-spirited, rollicking, demonstrative students, through the days and nights of drudgery and obstetrical service in La Maternité in Paris to the time when she walked the streets of New York City in a vain attempt to rent office space where she would be allowed to hang out a sign, no matter how diminutive it might be, tested deep resources of courage.

When she first came to Geneva, Elizabeth Blackwell's position among the students, as well as among the lay population of the town, was that of an immoral or insane woman. To combat such slander her only weapons were unobtrusive and simple humility, freedom from pride and arrogance. Her sweet reticence and simplicity at last won the battle—a battle in itself which if lost would have ended her hopes and aspirations.

Although these wounds to her pride and attacks upon her reputation were hard to bear, the load was lessened by demands made for work and more work. At night, alone in the college, tracing out the anatomical ramifications and distributions of the various structures in the body, she would suddenly be struck by the intense stillness and find that it was midnight and the rest of the little town was asleep. Her indefatigable industry was a healing balm for hurt feelings.

During her efforts to gain admission to a medical school and even oftener when she sought entrance into a hospital for practical work, many people had urged her to assume male attire and go to Paris for study. Of this she has said, "Neither the advice to go to Paris nor the suggestion of disguise tempted me for a moment. It was to my mind a moral crusade on which I had entered, a course of justice and common sense and must be pursued in the light of day and with public sanction in order to accomplish its end." Honesty, freedom from fraud, was an inherent part of her, which she demonstrated throughout her long life. Honesty, closely coupled with a sense of loyalty, was a natural attribute. Whether it was family loyalty, loyalty to her country, loyalty to sex or profession, every form of loyalty found her steadfast. Letters to her family during the trying student days, her return to her native land to help establish the Women's Medical College in London, obtaining a place as the first woman upon the English Medical Register, her assistance to women desiring to become physicians, all testify to her high standards of loyalty.

It was fortunate that her early dislike for medical subjects never brought any fear of disease or of personal injury. She wrote her thesis when in medical school on the epidemic cases of typhus that she had cared for while at Blockley Almshouse during her summer vacation. When on two occasions the hospital that Dr. Blackwell had established in New York City was attacked by an angry mob she smiled fearlessly, and the police, her staunch friends, quelled the riots.

Her personality never failed to bring her friends from among the most distinguished and famous as well as the lowly. It was Horace Greeley, Editor of the New York *Tribune,* who placed her professional card in his widely circulated paper when she was unable to rent an office and display her professional sign. Henry Ward Beecher opened a fair for the benefit of her hospital. Florence Nightingale found her a great inspiration. Lady Noel Byron, wife of the poet, kept up a lively correspondence with Elizabeth Blackwell after they parted in England, and much of it has been published. In 1869, on her return to England, she had a circle of acquaintances that

included Herbert Spencer, Charles Kingsley, Dante Gabriel Rossetti, Mrs. Jameson, the Herschels, and Faraday.

It is doubtful whether any future medical women will ever be able to make such contributions as Elizabeth Blackwell for the promotion of women in medicine. As a leader she drew under her influence such medical women as Marie Zackrzewska, Mary Harris Thompson, and Ann Preston, and together these four women, at a time when money was scarce and discrimination against women doctors acute, raised the necessary funds and built women's medical schools and hospitals staffed by women doctors in Philadelphia, Boston, New York, and Chicago.

As a teacher, lecturer and author, Elizabeth Blackwell surpasses all her women medical contemporaries. A closely printed page is required for a list of Dr. Blackwell's chief works given in her biography.

Through the full development of these chromosomes, especially leadership and creative power, Elizabeth Blackwell saw the number of women in medicine increase from one in 1849 to more than 500 in 1870. Every decade after that—1880, 1890 to 1900—saw a doubling in the number of medical women, until, in 1900, the number of women physicians in the United States reached nearly 8,000.

Since 1900, however, the number has not increased. There are still 8,000 women physicians, despite the fact that only three medical schools are now closed to women and a large percent of hospitals have extended opportunity to them.

In the last World War women were admitted for the first time to service in the Army and Navy and are still serving there in small numbers. A few women are teaching in co-educational medical schools, many have positions in public health service, and occasionally women physicians hold office in medical societies. In the nineteenth century Elizabeth Blackwell and her followers opened doors for the medical women of the twentieth century to enter and show by their performance the importance of keeping those doors open.

The Blackwell victory belongs not alone to the medical world, but to all vocations for women. While in 1849 there was only a handful of vocations for women, today—one hundred years later—there are 451, as taken from the May 1949 Census, and these 451 vocations are filled by over 16,000,000 women.

The century beginning with Dr. Blackwell's success in opening the medical field for women has been punctuated with the entrance of women into hundreds of other careers. She was gradually followed by the first woman lawyer, the first woman minister, the first trained nurse, the first woman typist, the first woman architect, the first woman mayor, the first woman foreign ambassador, the first woman member of the Cabinet—on and on, down to this year, when Mrs. Clark became the first woman Treasurer of the United States.

In this one hundredth year of the opening of vocations to the women of the world, let us strive to carry on the work, universal in scope, begun by Elizabeth Blackwell, as well as to cultivate all those qualities with which she was so generously endowed and which made her the woman of the century.

Current Publications of Women in Medicine

Fields, I. A., **Martin, Helen Eastman**, Simonsen, D. G. et al.: The treatment of acute anuria with evaluation of peritoneal lavage, Ann. Surg. 129:445-462, April 1949.

(From Department of Surgery, College of Medical Evangelists, Department of Medicine, School of Medicine, University of Southern California, and Los Angeles County Hospital.)

Six patients with anuria due to potentially reversible tubular lesions were treated with peritoneal or gastric lavage. Three of these patients died and three lived. In addition, one patient who died of an acute diffuse glomerulonephritis was treated with peritoneal lavage. Peritoneal lavage was (1) effective in removing substantial amounts of nitrogenous waste products; (2) helpful in adjusting a disturbed electrolyte pattern, especially potassium; (3) an indirect means for supplying glucose. Its disadvantages were (1) a technical procedure requiring constant and expert supervision and special nursing; (2) peritoneal contamination; and (3) absorption of fluid from the peritoneal cavity if hypertonic fluids were administered simultaneously. Gastric lavage, used as the primary lavage method in one case, was much less effective but did not have the disadvantages of peritoneal lavage. Peritoneal or gastric lavage should be used only if the patient shows some deleterious effects from nitrogen retention or electrolyte disturbance, particularly hyperpotassemia.

Acute pulmonary edema was the immediate cause of death in 4 patients. Six of the 7 patients studied developed generalized edema at some stage. These facts emphasize the necessity for rigid restriction of fluid and sodium.

Work, Elizabeth: Estimation of ergothioneine in urine by paper partition chromatography, Lancet 1:652-654, April 16, 1949.

(From Department of Chemical Pathology, University College Hospital Medical School, London.)

This method of estimation is at best only roughly quantitative (more or less 50%) and as applied here is only comparative. The method was developed on short notice to follow the excretion of ergothioneine during clinical trials, since no other method was satisfactory. The numbers of urine samples which could be applied to the paper to test for minimal levels were limited by time and space. So far as the present figures go, the level of ergothioneine in normal urine lies between 130 and 300 mg. per litre. Sullivan and Hess (1933) estimate the amount of "ergothioneine-like material to about 90 mg. per litre of normal urine."

Lowenhaupt, Elizabeth: Absence of renal lesions in rats receiving a synthetic diet low in protein, Arch. Path. 46:398-399, Oct. 1948.

(From Division of Pathology, University of California, San Francisco.)

Author concludes that low protein intake is not responsible for the renal tubular lesion occurring in rats fed a low protein, carrot, and turnip diet. Chronically alkaline urine containing large amounts of calcium and phosphates is suggested as the basis for the precipitation of calcium in the tubules, with a foreign body reaction occurring about the cast. An identical lesion is described in chronic alkalosis and is produced in the rat by a chloride-deficient diet.

Silberberg, M., and **Silberberg, Ruth:** Role of age in estrogen-induced lymphoid tumors of mice, Arch. Path. 47:340-349, April 1949.

(From Snodgras Laboratory of Pathology, St. Louis City Hospital.)

The susceptibility of male mice of strain C3H to estrogen induction of cancerous lymphoma varied with the age at which the administration of the estrogen (alpha estradiol benzoate) was begun. A maximum susceptibility was found about the onset of sexual maturity. The effect of castration at various ages (3 to 4 weeks to 4 months and over) was studied with regard to administration of the estrogen. An extratesticular age factor, presumably residing in the aging hemopoietic tissues, aids in determining the outcome of this type of leukemogenesis. The significance of the age factor varies in different strains and seems to decrease as the genetic susceptibility of the animals to estrogen induction of cancerous lymphoma increases.

Jaffe, E. R., **Humphreys, Eleanor M.**, Benditt, E. P., and Wissler, R. W.: Effects of various degrees of protein depletion on histologic and chemical structure of rat liver, Arch. Path. 47:411-423, May 1949.

(From Department of Pathology, University of Chicago School of Medicine.)

This experiment on young adult male rats illustrates the histologic and chemical changes which occur in the livers of animals restricted to a low protein diet for variable periods. An initial fall in tissue mass parallels a decrease in lobule and cell size with the appearance of a small droplet fatty change. A secondary rise in liver weight is associated with a disproportionate increase in fat which is reflected in a diffuse fatty alteration. Subsequent depletion reduces both the quantities of water, fat, protein, and water-soluble fraction, and the visible cell size and fat content. After prolonged protein deprivation another increase in stainable and chemically detectable lipids occurs, while marked atrophy of cytoplasm and irregularity of nuclear arrangement appear.

Despite the severity of the histologic and chemical alterations, the entire process quickly undergoes complete reversal when a diet containing a high quality protein is fed.

The mechanisms which operate in the production of the hepatic changes of the cachectic states associated with some human diseases may be similar to those operating to produce alterations observed here.

Zeckwer, Isolde T.: Proliferation of the epithelium of intrahepatic bile ducts in parabiotic rats following obstruction of the bile ducts, Arch. Path. 47:424-428, May 1949.

(From Department of Pathology, University of Pennsylvania School of Medicine.)

Experiments were made in which the common bile duct was cut between ligatures in a rat which was in parabiosis with a litter mate whose common bile duct was unobstructed. The experiments demonstrated the extreme proliferation of bile duct epithelium that can be maintained for periods up to 114 days. These are much longer periods than any during which the proliferation could be maintained in single jaundiced rats.

Keim, H. L., Frisch, D. C., and **Palmer, Alice E.:** Plasma protein and dermatitis, Arch. Dermat. & Syph. 58:314-334, Sept. 1948.

A case of intractable chronic disseminated neurodermatitis treated with high protein, high carbohydrate diet, and parenterally administered plasma and a protein hydrolysate is reported. The response was rapid and dramatic, but patient died 4 months later after abdominal surgical treatment. A case of

arsenical exfoliating exudative dermatitis responded to similar therapy after other treatment had failed. Two patients with chronic atopic eczema with exudation were promptly benefited by this therapy. No conclusions can be drawn from these few cases, but a possible therapeutic approach is suggested in cases of resistant disease in which significantly lowered protein plasma levels are encountered. The theoretic action of protein, plasma, and protein hydrolysate in dermatitis is discussed. A series of correlative laboratory studies on a representative number of patients with chronic exudative exfoliating eruptions has been inaugurated in an attempt to clarify further the role of serum proteins in dermatitis.

Topper, Anne: Treatment of exophthalmic goiter in childhood. A report of a follow-up study in twelve cases, Am. J. Dis. Child. 76:26-43, July 1948.

(From Pediatric Service, Mount Sinai Hospital, New York.)

Of the 12 children seen during the past 25 years, 8 were treated conservatively and 4 were subjected to thyroidectomy. The periods of observation varied from three and one-half to twenty-five years. Of the 8 children treated medically, one died of an apparently unrelated condition, 10 years after all the symptoms of exophthalmic goiter had been arrested. One child was lost track of, but had been well for 3½ years. The other 6 are still under observation, having been followed from 5 to 25 years, and are entirely well and leading normal lives. Of the 4 children treated surgically, 3 have had occasional hypothyroidism, which responded readily to treatment. All four are doing well.

The pediatrician should continue the search for satisfactory medical treatment of exophthalmic goiter when it occurs before puberty.

Ash, Rachel: Rheumatic infection in childhood: fifteen to twenty year follow-up. Caution against early ambulant therapy, Am. J. Dis. Child. 76:46-52, July 1948.

(From Children's Hospital of Philadelphia and Department of Pediatrics, University of Pennsylvania Medical School.)

The results of a follow-up study of 331 rheumatic children fifteen years following the onset of their infection and of 150 children twenty years following the onset of their infection are presented. The incidence of carditis and of deaths during the first 10 years following onset was greater among children taken ill during the 1923-1927 period than during the years 1928-1932 and least of all among those taken ill during the years 1933-1937. Although a spontaneous change in the character of the disease has probably occurred during this period, the favorable influence of prolonged rest in bed at onset would seem to have also played a part. Pediatricians are urged not to institute early ambulant treatment in the care of the rheumatic child.

Meizlik, E. H., and Carpenter, Anna-Mary: Beneficial effect of measles on nephrosis. Report of three cases, Am. J. Dis. Child. 76:83-90, July 1948.

(From Departments of Pediatrics and Pathology, University of Pittsburgh, and Children's Hospital of Pittsburgh, Pa.)

In 3 children with nephrosis, spectacular and apparently permanent improvement occurred after intercurrent infection with measles. The measles occurred during the early stages of the nephrotic syndrome. Hydrolysate of lactalbumin prescribed during and following measles is a possible beneficial contributory factor. The improvement has been maintained for nine months.

Neale, A. E., and Menten, Maud L.: Tumors of the thymus in children, Am. J. Dis. Child. 76:102-108, July 1948.

(From Department of Pathology, University of Pittsburgh, and the Children's Hospital of Pittsburgh, Pa.)

Two cases of tumor arising in the thymus are reported and the literature is briefly reviewed. The rarity of thymic neoplasms in children is emphasized.

Fashena, Gladys J.: Mechanism of hyperbilirubinemia in the newborn infant. Experimental demonstration of functional hepatic immaturity, Am. J. Dis. Child. 76:196-202, Aug. 1948.

(From Departments of Pathology and Pediatrics, Southwestern Medical College of Southwestern Medical Foundation.)

Twenty-one consecutive normal newborn infants, weighing between 3,200 and 3,400 gm., were followed from the day of birth until their discharge from the hospital nursery on the sixth or seventh day of life, by means of daily red blood cell counts and determinations of hemoglobin concentration, red cell volumes, and plasma bilirubin levels. In all but one instance, the bilirubin content of the meconium excreted during the first three days of life was determined. For a similar series of 50 normal infants a daily estimation of plasma bilirubin was made; in each instance the infant's and the mother's blood type and Rh type were determined, and a search was made for antibodies to A, B, and Rh antigens. No demonstrable relation was found between the magnitude of the drop in red blood cell count and packed red cell volume and the degree of hyperbilirubinemia developing early in postnatal life. The amount of bile pigment in the first meconium and the height to which plasma bilirubin rose during the first weeks of postnatal life showed an inverse correlation suggesting functional immaturity of the liver operating before birth as a cause for elevated serum bilirubin levels in the cord blood. Direct assessment of hepatic function in infants exhibiting hyperbilirubinemia showed pronounced impairment of hepatic function and normal excretory function in infants of a comparable group without hyperbilirubinemia. The plasma bilirubin pattern in infants compatible with their mothers and those incompatible with respect to A, B, and Rh factors did not differ. Insoimmunization, therefore, does not appear to play a part in the production of physiologic hyperbilirubinemia in the newborn. The evidence points to functional immaturity of the liver operating before birth and for a variable period after birth as the cause of bilirubin retention in the neonatal period.

de Bruyn, Willemina M., Kerteweg, R., and van Waveren, E.: Transplantable mouse lymphosarcoma T 86157 (MB.). Studied in vivo, in vitro and at autopsy, Cancer Research 9:282-293, May 1949.

(From Laboratory of the Antoni van Leeuwenhoekhuis, Netherlands Cancer Institute, Amsterdam.)

By means of tissue culture and transplantation experiments and in vivo studies including gross and microscopic anatomy and hematology, it was proved that mouse lymphosarcoma T86157 (MB) is a real tumor. The malignant cell of this tumor is a pathologic lymphoblast. No filterable tumor-inducing virus could be detected.

Dodd, Katharine, Johansmann, R. J., and Rapoport, S.: Thrombosis of the vena cava and hepatic veins (Chiari's syndrome) in a patient with nephrosis. Report of a case and observation on serum phosphatase and prothrombin time of plasma, Am. J. Dis. Child. 76:316-325, Sept. 1948.

(From Children's Hospital Research Foundation and Departments of Pediatrics and Pathology, Uni-

versity of Cincinnati College of Medicine, Cincinnati, Ohio.)

In this case thrombi were also present in the renal veins and in the portal area. Great increase in the serum phosphatase occurred in the course of the disease. Observations are also recorded on the prothrombin time of 6 patients with nephrosis. The clotting time of undiluted plasma was observed to be variable, but the slope of the dilution curve was always reduced.

Lincoln, Edith M., and **Kirmse, T. W.:** Streptomycin and promizole in miliary tuberculosis and tuberculous meningitis in children, Lancet 1:767-773, May 7, 1949.

(From Department of Pediatrics, New York University, and Children's Medical Service, Bellevue Hospital, New York.)

Of 7 cases of miliary tuberculosis treated with promizole, none developed clinical meningitis. Five survived 2 to 4 years, free from evidence of miliary tuberculosis. Of 10 patients treated simultaneously with streptomycin and promizole, one died after 6 days' treatment and another of a relapse from meningitis 11 months after the initial diagnosis of miliary tuberculosis. No relapse of miliary tuberculosis has occurred in the survivors of either group. Of 18 patients with tuberculous meningitis treated with intramuscular and intrathecal streptomycin and with promizole by mouth, 13 were living 3 to 21 months later. There have been no serious neurological sequelae. Three cases relapsed 25 to 43 days after completion of therapy. Tubercle bacilli fully sensitive to streptomycin were cultured from the C.S.F. of each of the three cases during the first week of relapse. The evidence presented indicates that the addition of promizole to streptomycin is of value in the treatment of miliary tuberculosis and tuberculous meningitis.

Arey, S. L., and **Christiansen, Mary P.:** Advantages of a separate nursery for premature infants, Minnesota Med. 32:384-385 and p. 387, April 1949.

(From Department of Pediatrics, University of Minnesota, Minneapolis.)

A comparison of the results before and after the establishment of a separate premature nursery revealed a lowering of premature mortality by approximately one-half. Care by interested graduate nurses in a separate nursery is a most important factor in lowering the death rate among premature infants.

Buxton, P. H., **Simon, Rosemary D.,** and Selbie, F. R.: Streptomycin in non-tuberculous infections, Lancet 1:729-733, April 30, 1949.

Streptomycin was given in 67 cases of infection by organisms insensitive to the sulfonamides and penicillin but sensitive to streptomycin. Relatively large doses limited to a 4-day course in urinary infections due to susceptible organisms are likely to cure about one third of the cases, provided there is no mechanical obstruction to drainage producing an inaccessible nidus of infection. In staphylococcal infections resistant to other forms of chemotherapy the use of streptomycin has been promising. Side reactions were encountered in less than a third of the cases and in only 3 cases where there was severe vestibular disturbance were they of any serious significance.

Doyle, G. B., and **Frodshan, Patricia:** Fatal air embolism during blood transfusion, Lancet 1:735-736, April 30, 1949.

A fatal case of air embolism followed the use of a Higginson syringe to expedite a blood transfusion. The explanation advanced is that the blocking of the lower part of the filter by blood-clot allowed air instead of blood to pass into the patient when the pressure inside the bottle was raised.

Jubelirer, R. A., and **Glueck, Helen I.:** Capillary fragility studies (Gothlin test) on one hundred patients receiving dicumarol, J. Lab. & Clin. Med. 34:448-457, April 1949.

(From Department of Internal Medicine, The Jewish Hospital, Cincinnati, Ohio.)

These patients were studied to determine if any correlation exists between the occurrence of hemorrhage and increase of capillary fragility as measured by the Gothlin test. Six patients received dicumarol continuously; the shortest period being 3 months, and the longest, 19 months. None of these demonstrated a positive Gothlin test. Hemorrhage was observed 7 times in 100 cases. In none of these was the Gothlin index positive. On the other hand no evidence of hemorrhage was observed in 7 patients who demonstrated a positive Gothlin. The interpretation of the various tests for the detection of increased capillary fragility is briefly discussed and the pathologic findings of hemorrhage occurring with dicumarol are reviewed. The study suggests that the status of the cutaneous capillaries as detected by the Gothlin test does not reflect alterations which may occur in other portions of the capillary bed. Careful clinical observation and meticulous laboratory control are necessary to detect and prevent hemorrhage in patients receiving dicumarol.

Ruskin, S. L., and **Merrill, Alice T.:** Newer studies of iron ascorbate, Am. J. Digest. Dis. 16:182-188, May 1949.

The chemical relationship between iron and the ascorbate radical was studied. The behavior of solutions of ferrous sulphate and ascorbic acid were quite different from that of ferrous ascorbate. The presence of free acid leads to a more rapid breakdown of ascorbic acid, similar to that of a high alkaline reaction. The near neutral pH ferrous ascorbate was more stable than either extreme. Iron ascorbate is a labile ferri-ferro complex.

The authors present an explanation for the rapid drop in plasma vitamin C level after the intravenous introduction of iron. They also point out the role of the coupled oxidation of oxyhemoglobin and ascorbic acid and the relationship of the stroma factor to cancer anemia.

Spivack, Mary: Shedding of decidua during uterine pregnancy and its clinical significance, Am. J. Obst. & Gynec. 57:989-995, May 1949.

(From Obstetric Departments of Mount Sinai Hospital and The Chicago Medical School, Chicago, Ill.)

A case is reported in which decidual tissue was found in the cervical canal of an early pregnancy and resembled grossly fetal membranes. The diagnostic pitfalls are emphasized and their avoidance discussed. Author concludes that if the source of every bleeding in pregnancy be determined and the histologic character of every tissue expelled be investigated, then some operative deliveries could be avoided and some pregnancies salvaged. An accurate diagnosis and knowledge of the underlying pathology are essential for the intelligent management of such cases.

Pirani, C. L., Ewart, F. E., Jr., and **Wilson, Audrey L.:** Thromboendarteritis with multiple mycotic aneurisms of branches of the pulmonary artery, Am. J. Dis. Child. 77:460-473, April 1949.

(From Departments of Pathology, Pediatrics, and Roentgenology, University of Illinois College of Medicine.)

A case of thromboendarteritis of the pulmonary arteries with multiple mycotic aneurisms within the

lungs is reported and the clinical, pathologic, and roentgenologic aspects of this condition are briefly discussed. The condition is extremely rare, occurring more frequently on the basis of bacterial endocarditis and only exceptionally on the basis of thrombophlebitis, as in this case. The clinical and roentgenologic findings are not characteristic, and cases in which the diagnosis was made in life have not been reported. Such a diagnosis, however, should be thought of in cases of bacterial endocarditis and chronic thrombophlebitis when pulmonary symptoms, such as hemoptysis, associated with atypical pulmonary shadows in the roentgenograms of the chest are observed.

Morgan, Isabel M.: Mechanism of immunity in poliomyelitis and its bearing on differentiation of types, Am. J. Med. 6:556-562, May 1949.

(From Poliomyelitis Research Center, Department of Epidemiology, Johns Hopkins University, Baltimore, Md.)

The concept of immunity to poliomyelitis as developed in the last few years is presented. This concept has been based largely on experimental work with monkeys and chimpanzees and, for certain purposes, cotton rats and mice. Direct observations on human beings are also discussed.

Hortsmann, Dorothy M.: Clinical aspects of acute poliomyelitis, Am. J. Med. 6:592-605, May 1949.

(From Section of Preventive Medicine, Yale University School of Medicine, New Haven, Conn.)

The more workable classification of clinical forms of poliomyelitis into abortive, non-paralytic, and paralytic types, is used in this discussion. The types are defined and described. The incubation period, history, symptoms in the different age groups, the physical examination, clinical laboratory findings, differential diagnosis, medical treatment, prognosis, and clinical immunity are considered.

Wittman, Phyllis: A classification of normal, maladjusted and disordered personality types. III. Intelligence disorders, Am. J. Ment. Deficiency 53:610-616, April 1949.

(From Department of Public Welfare, State of Illinois.)

This paper presents one part of a proposed classification of normal, maladjusted, and disordered personality types, attempting to correct the obvious inconsistencies of the A.P.A. classification, to recognize maladjusted and disordered reactions as relatively exaggerated, uninhibited expressions of the same personality reactions shown by "normal" personalities, to recognize the significance of both psychic and somatic factors and their inter-relationships in personality, and to provide quantitative, i.e. numerical, designations that can be clearly defined and that lend themselves readily to systemization and to statistical manipulation. The author proposes a classification of intellectual disorders subdivided into three sub-groups: (A) Intellectual Capacity (Quantitative) that indicates the level of present functioning for both amentia and dementia, as high grade, middle grade, or low grade; (B) Intellectual Capacity (Qualitative) to classify the type of amentia; and (C) Intellectual Efficiency to describe the type of dementia.

Mahler, Margaret S., Ross, J. R., Jr., and De Fries, Zira: Clinical studies in benign and malignant cases of childhood psychosis (schizophrenia-like), Am. J. Orthopsychiat. 19:295-304, April 1949.

(From New York State Psychiatric Institute and Columbia University, New York.)

The authors present in condensed outline, the pathognomonic clinical symptoms of psychosis in children, and also refer to and illustrate several genetic, structural, and dynamic considerations derived from their psychoanalytic approach. They studied 16 cases of psychotic children ranging in age from 3¼ to 9½ years. The children in 5 instances were treated for 1½ to 5 years by a modified technique of child analysis. They emphasize that the psychotic process acts upon the personality of a child, in whom organization of the ego and superego is in process of growth, and whose hold on reality is not consolidated. These factors create inestimable additional difficulty in differential diagnosis, in evaluation of pathognomonic signs, and in the evaluation of malignancy or benignity of the process.

Cushing, J. G. N., and Cushing, Mary McKinniss: A concept of the genesis of hostility, Bull. Menninger Clin. 13:94-99, May 1949.

Authors attempt to show that the genesis of hostility is in prenatal life and that it is quite possible for the feeling of hostility to be laid down as an engram in consciousness before birth; also that the postnatal reaction is merely a continuance of the earlier pattern. They state that it is even possible that this latent hostility may be the "original sin" with which philosophers and theologians have been preoccupied for centuries, and for which they have prescribed the antidote of love.

Halsted, J. A., Van Amerongen, Suzanne Taets, and Silbert, Annette: Clinical and psychologic aspects of cardiospasm, Bull. New England M. Center 11:68-74, April 1949.

The etiology of cardiospasm is unknown. Evidence from the literature regarding pathologic psyhiology points to an abnormal innervation of the entire esophagus with disordered or absent peristalsis and an abnormal response to parasympathomimetic drugs. No conclusive evidence is available that psychologic factors are the cause of the disease, but there is ample foundation for the belief that the emotions profoundly influence the symptomatology and clinical course in many cases. Psychotherapy is of great importance in treatment. In at least six of seven cases being studied, emotional disturbances appeared to be of clinical importance.

Seligman, A. M., and Ashbel, Rivka: A new reagent for the histochemical demonstration of active carbonyl groups of lipoid and nonlipoid material, Bull. New England M. Center 11:85-86, April 1949.

This reagent (2-hydroxy-3-naphthoic acid hydraxide) is described. It reacts with carbonyl groups but in addition couples with a diazonium compound (tetrazotized diorthoanisidine) to give an insoluble blue compound. This is expected to increase the sensitivity of the ketosteroid method and improve the optical effects. By this method the carbonyl groups of lipoid in formalin-fixed adrenal cortex, corpus luteum, testicular interstitial cells, and synctial trophoblasts of the placenta were visualized. Other uses for the reagent are also described.

Boyd, Gladys L.: Streptomycin in childhood tuberculosis, Canad. M. A. J. 60:476-480, May 1949.

(From Hospital for Sick Children and Department of Paediatrics, University of Toronto, Toronto, Canada.)

Observations made since Jan. 1, 1947, on 34 children treated with streptomycin, are presented. The expected mortality of the groups was at least 80% while the real death rate was 16%. In the author's experience, streptomycin therapy has materially reduced the mortality in virulent forms of childhood tuberculosis. The drug has permitted cure of all pulmonary cases treated so far, and there is evidence to support the claim that it cures tuberculous meningitis. Better selection of cases of tuberculous meningitis to be treated will result in better end results.

Warner, Marie Pichel: What's new in the diagnosis and treatment of the infertile female, M. Women's J. 56:25-29, & 64, New York, N. Y., May 1949.

General discussion of new developments and attitudes.

Glasgow, Maude: Do women need protection? M. Woman's J. 56:35-38, & 63, May 1949.

Stricter legal measures should be undertaken to prevent the increase in sex crimes. Women should take the initiative in seeing that the sex offender is swiftly brought to trial and given treatment or punishment. Above all such offenders should not be permitted to roam the streets freely after once convicted of such crimes.

Topper, Anne: Graves' disease in children, J. Am. M. Women's A. 4:181-184, May 1949.

(From Growth and Development Clinic of the Mount Sinai Hospital, New York.)

When Graves' disease occurs in childhood it should be treated conservatively whenever possible. Since the symptoms in most cases appear in the prepuberty period, they must be tided over by conservative management until the establishment of puberty brings with it a spontaneous arrest of the symptoms. Conservative management includes rest, proper diet with adequate vitamin intake, especially of vitamin B, psychotherapy where indicated, and as needed some drug to control the synthesis of the thyroid hormone. Whether this drug be propylthiouracil, radioactive iodine, or some other as yet unknown compound is unimportant. The important thing is to continue the search for a satisfactory medical treatment of Graves' disease in children and to avoid surgery wherever possible.

Tyson, Mary C.: The Rh factor, J. Am. M. Women's A. 4:185-187, May 1949.

(From the Mount Sinai Hospital, New York.)

The subject is discussed in general, and suggestions are made for observing and treating infants born of a mother with anti-Rh factor in her blood. The author emphasizes that laboratory techniques of Rh typing and antibody determination are treacherous and it is therefore important to have well-run central laboratories to work exclusively on this subject.

Strauss, Lotte, and Shwartzman, G.: Vitamin B6 deficiency in the Syrian hamster, J. Am. M. Women's A. 4:187-188, May 1949.

(From Department of Bacteriology, The Mount Sinai Hospital, New York.)

The effects of vitamin B6 deprivation ranged from mild growth retardation to complete arrest of growth accompanied by severe malnutrition and cachexia and often by conspicuous fur changes. Treatment of the animals with pyridoxine, after prolonged deficiency, resulted in a prompt growth response, return of appetite, and restoration of normal fur and behavior. The postmortem findings in pyridoxine-deficiency hamsters are described.

Kanof, Naomi M.: Recent Advances in dermatology, J. Am. M. Women's A. 4:189-191, May 1949.

General discussion.

Fish, Gladys A.: A case of absent vagina, J. Am. M. Women's A. 4:192, May 1949.

(From the Mount Sinai Hospital, New York.)

Case report.

Claman, Leoni N.: Allergy, J. Am. M. Women's A. 4:193, May 1949.

Report of 5th annual meeting of American Academy of Allergy, Atlantic City, Dec. 6-8, 1948.

Carruthers, C., and **Suntzeff, Valentina:** Studies with the polarograph on the lipids of epidermis during normal and rapid growth, Cancer Research 9:210-214, April 1949.

(From Department of Anatomy, Washington University School of Medicine, St. Louis, Mo.)

Polarography of material extracted from tissues with alcohol and ether was studied in a mixture of unbuffered and buffered solution, dioxane, and tetrabutylammonium iodide. Evidence was presented to show that an alteration in the structure of a compound or compounds extractable from mouse epidermis and carcinomas by lipid solvents occurs during the process of epidermal carcinogenesis in mice. The lipids of hyperplastic epidermis behaved polarographically as did those of normal epidermis. The half-wave potentials of the reducible substances of epidermal lipid were shown to be dependent upon the pH of the solution employed for electrolysis. The half-wave potential of a compound characteristic of mouse skeletal muscle, liver, squamous cell carcinomas, and perhaps other organs was found to be pH dependent. The reducible compounds of mouse and human epidermal lipid appear to be the same. The process of epidermal carcinogenesis in both species seems to be similar with respect to the polarographic behavior of the lipids.

Dulaney, Anna Dean, Goldsmith, Y., Arnesen, K., and Buxton, L.: A serological study of cytoplasmic fractions from the spleens of normal and leukemic mice, Cancer Research 9:217-221, April 1949.

(From Sloan-Kettering Institute for Cancer Research, New York.)

Mitrochondria and submicroscopic particle fractions from the spleens, livers, and kidneys of normal and leukemic mice are of complex nature in that they possess organ species and tissue fraction-specific antigens. All except the liver fractions possess in addition the Forssman antigen. Antisera to the spleen fractions show substantially greater reactivity for the spleen cytoplasmic antigens than for the liver and kidney fractions. Antisera to all of the mitochondria and submicroscopic particle fractions of both normal and leukemic spleens show greater reactivity for the leukemic than for the normal components. These antisera exhibit specificity of reaction with homologous mitochondria and submicroscopic particle fractions. The nature of these differences must be established by further work.

Craig, W. S., **Naish, F. Charlotte,** and Buchanan, M. F. G.: Instruction of the medical student in paediatrics. An insight into family practice, Brit. M. J. 1:801-803, May 7, 1949.

An educational experiment is described which is intended to offset the difficulties, at least in part, of giving the medical student practical insight into conditions prevailing in family practice. It is considered that the experiment has been a success, is capable of further development, and might be extended to a wider field of medical training than that concerned solely with health and disease in childhood.

Esselborn, Virginia M.: Hormonal control of the menstrual cycle, application of physiologic concepts to therapy, Cincinnati J. Med. 30:248-250, May 1949.

(From Department of Medicine, University of Cincinnati College of Medicine, and Cincinnati General Hospital, Cincinnati, Ohio.)

The physiology of the menstrual cycle is briefly outlined. The etiology and pathological physiology of certain irregularities of bleeding are described. Treatment of these irregularities should be on a psysiologic basis designed to imitate and eventually restore normal function. Such treatment is outlined.

Ross, Mabel: Modifiable factors in anxiety reactions, Dis. Nerv. Syst. 10:146-150, May 1949.

(From Prince George County Mental Health Clinic, Maryland.)

Although the anxiety reactions of children develop in a setting of disturbed family relationships, the stresses and strains of the community often increase the severity of these reactions. No treatment of the child can be effective without the parent entering into the treatment plan but beyond the direct control of the parent are many community factors which can be modified to give the patient more opportunity of continuing improved adjustment. It is in this area that "preventive psychiatry" becomes important. Illustrative case histories are cited.

Almy, T. P., Hinkle, L. E., Jr., Berle, Beatrice, and **Kern, F., Jr.:** Alterations in colonic function in man under stress. III. Experimental production of sigmoid spasm in patients with spastic constipation, Gastroenterology 12:437-449, March 1949.

(From Department of Medicine, New York Hospital and Cornell University Medical College, New York.)

In 39 patients with spastic constipation or colonic pain, the motility of the sigmoid colon was studied by proctoscopy or by inlying balloons. When subjected to cold pain, painful compression of the head, or the discussion of life situations productive of emotional conflict, these patients often exhibited markedly increased motility of the colon. This change was associated with obvious changes in speech or in behavior indicating that the patient was under stress. The results are similar to those obtained earlier with persons having no clinical disorder of the colon.

Margolis, B., Valdes-Dapena, Marie, and **Boles, R. S.:** Peptic ulcer in infancy. Report of a case with hemorrhage and perforation, Gastroenterology 12:489-494, March 1949.

(From Departments of Pediatrics, Pathology, and Medicine, Philadelphia General Hospital, Pa.)

In this case hemorrhage and perforation had occurred. The postmortem findings are also described. Etiology, symptomatology, and treatment of peptic ulcer in infancy are briefly discussed.

Weyl, Ruth: Modern trends in anesthesia, J. Indiana State M. A. 42-425-433, May 1949.

Advances and trends are discussed with respect to drugs used, anoxia, hypoxia, atelectasis, and general physiology. Today the anesthesiologist, being an expert in judging and handling respiratory conditions, is called in as a consultant for all kinds of respiratory difficulties. He is called upon to administer therapeutic blocks. He is the judge of pre-and postoperative sedation, and of fluid administration during anesthesia. He is able and willing to procure adequate and safe anesthesia, and to take the entire responsibility for it, thus relieving the surgeon and allowing the latter to give his full and undivided attention to his important and specific task.

Coover, Lillian Storms: Nutrition-trained women in business, J. Am. Dietet. A. 25:530-534, June 1949.

Early pioneers in the field and present day workers have greatly influenced public thinking with respect to nutrition problems.

Burton-Bradley, Claudia: Infantile cerebral palsy, M. J. Australia 1: 413-414, March 26, 1949.

The term is defined. The distribution, etiology, history, clinical types, pathological physiology, treatment, diagnosis, and prognosis are very briefly discussed. In suggesting an approach to the problem, the author recommends first, early diagnosis; secondly, investigation of the child's intelligence and special senses, and also the etiology. The etiology is important in relation to the question of the parents having further children. Thirdly, she recommends that the children be classified according to intelligence. The educable, i.e. those with an intelligence quotient of 70 or over, should be educated and treated. Those with quotients from 70 to 50 should be treated and trained. Those with intelligence quotients below 50 should be considered with respect to the social and psychological aspects of the family, and, if these are applicable, should be directed to a mental institution.

Gillette, Harriet E.: The physician's responsibility in cerebral palsy, South. M. J. 42:411-415, May 1949.

The general problems of diagnosis and rehabilitation are discussed with specific recommendations. The attitude of the physician is important. The parents of the cerebral palsied patient also require understanding, patience, and psychology. They should understand what is being done for the child. The physician's responsibility to his patient does not end when the infant has been diagnosed, the child treated, and the youth educated and prepared for a vocation. Employers must be persuaded to make use of such a personality, and patients who have the initiative to set up a business for themselves should be encouraged to do so. Thus the greatest responsibility lies in knowing and understanding the problems of the children, recording the data and furthering research in prevention.

Dunning, Marcelle F, and **Kuttner, Ann G.:** Standard, unipolar limb and precordial leads in children and adolescents with inactive rheumatic fever, Am. J. Dis. Child. 77: 610-624, May 1949.

(From Irvington House, Irvington-on-Hudson, N. Y.)

The value of standard, augmented unipolar limb and precordial electrocardiograms as a means of determining cardiac hypertrophy was studied in 156 children and adolescents in the quiescent stage of rheumatic fever. A P wave of 0.10 second or more in the standard leads is a useful indication of auricular hypertrophy. Augmented unipolar limb leads are of aid in the interpretation of axis deviation. Electrocardiographic evidence of right ventricular hypertrophy is most readily demonstrable by means of unipolar precordial leads, and the condition may occur in the absence of, or concomitant with, left as well as right axis deviation. Definite criteria for the electrocardiographic diagnosis of left ventricular hypertrophy in young persons with rheumatic heart disease have not been established. However, high voltage in the augmented unipolar limb leads accompanied with the pattern of left ventricular hypertrophy in the unipolar precordial leads possibly indicate hypertrophy of the left ventricle.

Thelander, H. E., and **Goebel, Grace:** Microcephalia as a complication of pneumococcic meningitis. Am. J. Dis. Child. 77: 642-646, May 1949.

(From the Children's Hospital, San Francisco.)

A severe case of pneumococcic meningitis in an infant 2½ months old treated with penicillin and sulfadiazine with the disappearance of the organisms and the final clearing of the spinal fluid, but with resultant microcephalia, amentia, and death is reported.

Scharnagel, Isabel M. and **Pack, G. T.:** Multiple basal cell epitheliomas in a five year old child. Am. J. Dis. Child. 77: 647-651, May 1949.

(From Baby Clinic of Mixed Tumor Service, Memorial Hospital for Treatment of Cancer and Allied Disease, New York.)

This case is reported because it is the only one of its type that has been seen in a large tumor clinic for babies.

Mahler, Margaret S.: Discipline and punishment, Child Study. *26:* 69-71, 81-82, Summer 1949.

(From Columbia University, College of Physicians and Surgeons, and Children's Service, New York State Psychiatric Institute.)

Punishment should be adapted to each child as an individual. Its effect on the child is discussed. The author feels that the most important task may be to restore and maintain parents' confidence in their own role, enabling them to manage the every-day problems in bringing up their own children with greater security and satisfaction.

Greisheimer, Esther M.: The physiological effects of anesthesia, Am. J. Nursing *49:* 337-343, June 1949.

(From Temple University School of Medicine.)

The reactions of the nervous system, the respiratory, circulatory, and gastro-intestinal tracts, and the excretory system to anesthesia are described. The fluid balance, early ambulation, and the results of post-anesthesia observation rooms are discussed.

Klien, Bertha A.: Histopathologic aspects of retrolental fibroplasia, Arch. Ophth. *41:* 553-561, May 1949.

(From Department of Ophthalmology, Northwestern University Medical School, Chicago.)

Three cases are described and the significance of the findings are discussed with respect to the possibility of future therapy in such cases.

Mayo, C. W., and **Rice, Roberta G.:** Situs inversus totalis. A statistical review of data on seventy-six cases with special reference to disease of the biliary tract, Arch. Surg. *58:* 724-730, May 1949.

(From Division of Surgery, Mayo Clinic, Rochester, Minn.)

Of 1,551,047 patients who registered at the Mayo Clinic from 1910 through 1947, 76 were found to have complete (abdominal and thoracic) situs inversus on the basis of physical or roentgenologic observations or both. This represents an incidence of about 1 in 20,000. Of these patients 47% underwent surgical treatment at the clinic or elsewhere. Two cases of congenita atresia of the bile ducts in infants with complete situs inversus are reported. Five patients with complete situs inversus had had disease of the gall bladder previously or at the time of admission to the clinic. Four of these had undergone cholecystectomy, while one did not have sufficient difficulty to warrant an operation. One of these cases is reported.

The possibility of situs inversus being present must always be kept in mind by the physician performing abdominal surgery.

Painter, Elizabeth E. and Brues, A. M.: The radiation syndrome, New England J. Med. *240:* 871-876, June 2, 1949.

(From the Argonne National Laboratory.)

The radiation syndrome produced by a single total-body thirty day LD_{50} of external radiation or of internal emitters of alpha or gamma rays is characterized by three separate and distinct periods: the initial shock reaction or radiation sickness, the acute, and the subacute. The initial shock may last from 3 to 48 hours. Occasionally rabbits and chickens die during the initial period. Other animals, such as dogs, rats, guinea pigs, and goats do not die, but show prostration, diarrhea, urination, lacrimation, and decreased food and water consumption. In addition, man and the dog often vomit. The acute period lasts from 9 to 21 days during which most of the animals die. The preterminal changes and the sharp delienation of the terminal signs are discussed in detail. Some of the radiation effects are directly due to destruction of certain tissue elements. Many others are indirect and may be attributed to infections, toxic agents, hypoxia, and other secondary factors. Animals surviving 30 days or more fall into the subacute category, where fluctuations of recovery and depression of the leukocytes do not permit the use of the white-cell count for determining the progressive changes of radiation damage. A severe anemia, emaciation, and graying of dark haired animals are the usual signs of the radiation syndrome in this phase. The chronic phase is characterized by shortening of life and sporadic increase in tumors.

Nearly every physiologic system shows damage after total-body irradiation. The effects are non-specific. Many of the same manifestations are shown in the animal organism by the administration of the nitrogen mustards or urethane, in anaphylatic shock, agranulocytosis, the "alarm reaction" of Selye, and benzol poisoning. Damage to the radiosensitive cells will explain a great part of the picture, but much further understanding of the syndrome is required in the interest of prevention and therapy.

Razzano, Carmen: Regional enteritis, New York State J. Med. *49:* 1329, June 1, 1949.

(From Nassau Hospital, Williston Park, New York.)

A case is reported of regional enteritis which was treated with surgery. The acute phase of the disease is usually mistaken for acute appendicitis. In this case, a diagnosis of mesenteric thrombosis was entertained in view of the cardiac status. Penicillin and sulfadiazine had no effect in arresting the progress of the disease. While a recent review of the literature reveals that antibiotics are helpful in the acute phase of regional enteritis, surgery is the only method of therapy in the chronic obstructive stage, with or without fistula and abscess formation.

Neira, Edith: Consideraciones sobre un brote de encefalitis, Rev. chilena de pediat. *20:* 101-110, March 1949.

(Hospital Roberto del Rio.)

The clinical charts of 891 children who consulted the outpatient department over a period of 12 months, were studied. Of these, 91 were of children with a condition attributable to a neurovirus (55 had poliomyelitis; 12, peripheral facial palsy; 3, polyneuritis; 1, neuromyositis; and 20, acute encephalitis). Most of the children were over 2 years of age and became ill during the months of February and March. Although there was no characteristic picture the following syndrome predominated: marked drowsiness, convulsions, slight meningeal signs of short duration, vomiting, headache, and ocular signs. The cerebrospinal fluid was analyzed in 15 cases and was slightly changed in 10 and normal in 5. Of 17 children followed up, sequelae have been found in 7, consisting of hemiparesis, localized convulsive movements, in one case a Parkinsonian syndrome and attacks of petit mal in another. Differential diagnosis should be made between the following: tuberculous meningitis, brain tumor, poliomyelitis, and postinfectious encephalitis. Treatment is symptomatic.

Russell, Dorothy S.: Malignant osteoclastoma and the association of malignant osteoclastoma with Paget's osteitis deformas. J. Bone and Joint Surg. 31-B: 281-290, May 1949.

(From Bernhard Baron Institute, London Hospital.)

Five cases are considered in detail here—two osteoclastomas of the upper end of the tibia, treated along parallel lines by curettage, irradiation, and amputation, in which metastasis supervened; and three osteoclastomas of histologically malignant character complicating osteitis deformans (Paget's disease). These cases are part of the material obtained in a survey of preserved material in the Bernhard Baron Institute

since 1907. The subsequent history of many of the patients is unknown, but two are alive and well 33 and 34 years after amputation.

Kountz, W. B., Chieffi, Margaret, and Kirk, E.: Serum protein-bound iodine and age, J. Gerontol. *4:* 132-135, April 1949.

(From Division of Gerontology, Washington University School of Medicine, St. Louis.)

A study was made of the serum protein-bound iodine, serum cholesterol and basal metabolic rate in 141 individuals, 73 men and 68 women, between 25 and 100 years of age. The average organic serum iodine value was 4.8 micrograms percent, both in the men and the women. In the men a gradual decrease in the organic serum iodine concentration was found with advancing years, whereas in the women no certain correlation between age and iodine concentration was noted. In both sexes a gradual and regular decline with age was observed. The organic iodine value of serum showed no correlation to the serum cholesterol level in either sex. The findings support the assumption of a decreased thyroid function in the men with age. (7 references; 1 figure).

Chieffi, Margaret, and Kirk E.: Chronaxie studies in thiamine deficient old individuals, J. Gerontol. *4:* 127-131, April 1949.

Chronaximetric determinations on the supinator longus and tibialis anticus muscles were performed in 25 old subjects with low blood thiamine values and in 25 old individuals with normal blood thiamine concentrations, using a condensor discharge type of chronaximeter. The studies failed to reveal any statistically significant difference between the mean chronaxie values of the two groups. The percentage distribution of the observed individual chronaxie values was likewise essentially similar. On the basis of these findings it may be concluded that chronaximetric determinations do not appear to be of value in the diagnosis of moderately severe thiamine deficiency in old individuals.

Austin, Elizabeth S.: A message to physical therapists, Physical Therapy Rev. *29:* 265-266, June 1949.

This address to the graduating class, School of Physical Therapy, Children's Hospital, Los Angeles, California, discusses the task of the individual physiotherapist and the responsibilities to the patients. The author stresses the qualities of mind and attitudes which make for a successful achievement of aims and a full confidence and pride in the profession.

Robinson, Alice M., and Goulden, F.: A qualitative study of urinary 17-ketosteroids in normal males and in men with prostatic disease. Brit. J. Cancer. *3:* 62-71, March 1949.

(From Pathology Department, St. Bartholomew's Hospital, London, E.C.1.)

Methods for the chromatographic separation and estimation of 17-ketosteroids in urine extracts are discussed, and a standard technique which yields reproducible analysis is described. Urines from 19 normal males (ages 3-73 years) and urines from two cases of benign hyperplasia of the prostate and from 6 cases of caricinoma of this gland were examined by the method. In normal males the amounts of androsterone and of aetiocholan- 3 (x) -ol-17-one are approximately equal, but in prostatic disease the latter substance is present in relative excess. The significance of the observation is discussed.

Hoch-Ligeti, Cornelia, Hoch, H., and Goodall, K.: Investigations on the serum proteins in rats during the development of hepatic tumours due to feeding p-dimethylaminoazobenzene, Brit. J. Cancer *3:* 140-147, March 1949.

(From Radiotherapy Department, London Hospital, and Department of Chemical Pathology, London Hospital Medical College, London, E.1.)

The serum proteins of rats fed p-dimethylaminoazobenzene increase rapidly at the time of manifestation of the tumor. The increase is independent of the size of the tumor. The serum proteins drop to low levels when the health of the animals deteriorates. In the patterns of the normal rat sera electrolyzed in phosphate at pH 8.0 and M0.1, x,B- and globulin regions could be distinguished, and the albumin showed two components. The rats which developed tumors due to feeding pDA showed a relative and absolute increase in the globulins, mainly in the B and Y globulins. The concentration of albumin was unchanged, but generally the albumin peak was not resolved into two components. The possibility of the changes in the serum proteins being an immunological reaction is discussed.

Levin, S. J., and Moss, Selma S.: Contact dermatitis from streptomycin, Arch. Dermat. & Syph. *59:* 663-664, June 1949.

Case report. The patch test with this agent gave a strongly positive reaction. Re-exposures produced a relapse, and avoidance of contact kept the patient free of symptoms for several months.

Hughes, J. G., Jordan, R. G., and Hill, Fontaine S.: Jet injection in pediatric practice, Pediatrics *3:* 801-812, June 1949.

From Pediatric Division, College of Medicine, University of Tennessee, Memphis.)

The technique of jet injection, represents the first fundamental change in the basic principles of injection in almost 100 years. The method described is relatively painless and practically innocuous to tissue and has technical simplicity. The authors present information dealing with depth of pentration of substances injected, pain response of children, local effects on tissues, blood levels of penicillin and of streptomycin given by jet injection, and clinical response of patients given penicillin by this technique. The need for chemical inertness of the metal used in the metapule, viscosity of material which can be injected, and the possibility of inadvertent intravenous injection are discussed. The proper instrument for children under 10 years is one of 75 pounds spring pressure and for older children 100 pounds spring pressure. With these strengths it has been possible to secure intramuscular injections in the deltoid and triceps areas, and subcutaneous injections in the lateral thigh area. Injections over large veins should obviously be avoided.

Jet injection offers promise in pediatrics because of its relative painlessness and may prove of value in mass immunizations, by avoiding transmission of viral agents by contaminated needles. Further investigations are indicated.

De Fuccio, C. P., and Dresner, Evelyn E.: Meningococcemia with meningitis accompanied by bilateral gangrene of the lower extremities (Waterhouse-Friederichsen syndrome). Pediatrics *3:* 837-838, June 1949.

(From Pediatric Department of Jersey City Medical Center, Jersey City, N. J.)

A case is reported in which amputation of the lower third of both legs was performed. The patient is living and in good health.

Andersen, Dorothy H.: Therapy and prognosis of fibrocystic disease of the pancreas, Pediatrics *3:* 406-417, April 1949.

(From Departments of Pediatrics and Pathology, College of Physicians and Surgeons, Columbia University, New York.)

The etiology of the respiratory lesion in fibrocystic disease of the pancreas is discussed with a summary

of the congenital and nutritional hypotheses. There is no morphologic evidence that a specific congenital abnormality exists in the bronchi or in their secretion. The microscopic appearance of the mucus does not resemble that of the contents of the pancreatic ducts but does resemble the mucus seen in some other clinical conditions, notably asthma. A physiologic congenital abnormality of the bronchi is possible but unproved. Evidence is presented that dietary therapy improves the growth curves of infants diagnosed and treated prior to infection. The absorption of vitamin A and presumably of other fat-soluble specific substances is affected by diet.

Twenty-two cases of fibrocystic disease without clinical evidence of respiratory infection are presented. Twenty-one of these were seen after penicillin became available but only 11 received it. The majority of the 22 patients were started on dietary therapy before a cough had been present for as long as two months. This record is presented as evidence in favor of a nutritional factor in the etiology of the respiratory infection.

Harris, T. N., **Harris, Susanna,** and Nagle, R. L.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. VI. Comparison of streptococcal antihyaluronidase with antibodies to other streptococcal antigens in the serum of patients with rheumatic fever and acute streptococcal infection: mucin clot prevention test, Pediatrics *3:* 482-503, April 1949.

(From Children's Hospital of Philadelphia (Department of Pediatrics, School of Medicine, University of Pennsylvania), Philadelphia General Hospital, and Children's Seashore House for Invalid Children, Atlantic City, N. J.)

Titrations of antibodies to four streptococcal antigens have been carried out in the sera of patients with rheumatic fever and of convalescents from streptococcal infections. These antigens are hyaluronidase, hemolysin, and two somatic fractions, the cytoplasmic particles and supernate proteins. Mean titers to all of these were elevated in both rheumatic and streptococcal infection, being somewhat higher in rheumatic than in streptococcal infection in the case of three of these antibodies. In the fourth, antihyaluronidase, this difference was considerably greater. The antihyaluronidase titer showed better correlation with changes in the activity of the rheumatic infection than did the other tests, but there was no striking correlation between this titer and the severity of the illness.

Application was made of these findings to the problem of laboratory diagnosis of rheumatic fever by streptococcal serology. A method is presented for assessing the relative usefulness of such tests in terms of the distribution of their titers in this disease and in health. By this method the antihyaluronidase test was found to be the most useful of the four. (34 references; 7 tables; 3 figures).

Olmsted, R. W., **Svibergson, Ruth I.,** and Kleeman, J. A.: The value of rooming-in experience in pediatric training. Pediatrics 3: 617-621, May 1949.

(From Department of Pediatrics and Department of Obstetrics and Gynecology, Yale University School of Medicine, and University Service, Grace New Haven Community Hospital.)

An experimental four-bed rooming-in unit for mothers and newborn babies was inaugurated in 1946. Accompanying the unit, a rooming-in study group in the position of pediatric fellows was formed for the purpose of observing and recording certain factors relating to parent-child relationships in the new-born and infancy period. This has proved to be a fruitful period in which practical experience, research facilities, and teaching opportunity were well blended. This type of training combination is maximally effective only if there is a stable, directive nucleus to the study group which serves to orient the fellows and guide their research plan.

Because of its emphasis upon the understanding of the total individual, rooming-in has fostered a more mature and sympathetic insight into the patient. The more one learns of behavior, the more one is willing to accept deviations and to try to understand their causes. This consideration of the individual, with his own cultural milieu, family background, and personal experience, will broaden the pediatric approach.

Moloshok, R. E., Karelitz, S., and **Strauss, Lotte:** Homologous serum hepatitis in infants and children, Pediatrics 3: 651-666, May 1949.

(From Departments of Pediatrics and Pathology, Mount Sinai Hospital, New York.)

Eight cases are reported, 7 in infants under one year of age and one in a child of 2½ years. Five of these children died of acute hepatic degeneration. Suggestive evidence was presented implicating the icterogenic plasma in five cases. The clinical, laboratory, and postmortem findings of serum hepatitis are described in detail.

Benson, R. A., Schneider, Mae, and Brand, D.: The use of rice as a cereal food in infants. A clinical study, Arch. Pediat. 66: 209-211, May 1949.

(From Frederick S. Wheeler Foundation for Nutritional Research and Department of Pediatrics, New York Medical College, and Flower and Fifth Avenue Hospitals, New York.)

This is a preliminary study of the value of rice as a cereal food in a group of 78 normal children, carefully observed in the wards of a hospital. Rice as a cereal food appears to be well tolerated by infants, including the very young age groups below 3 months of age, with no occurrence of allergic or gastro-intestinal disturbances. Its value as a substitute or supplement to other cereal foods deserves attention.

Ettinger, Alice: Small intestinal pattern in sprue and similar deficiency diseases, Am. J. Roentgenol. 61: 658-670, May 1949.

(From Joseph H. Pratt Diagnostic Hospital.)

Roentgenological studies of the small intestine may help to establish conclusively the diagnosis of a deficiency state in cases in which a clinical diagnosis is difficult. Such studies might also contribute towards a better understanding of various nutritional disturbances other than sprue. In the author's series of 12 cases of deficiency diseases, the roentgenological findings gave the clue to the proper diagnosis in two, and possibly in a third. In these 3 cases, the classical clinical symptoms of sprue were lacking. There was abdominal distention and peripheral edema but no evidence of fatty stools and the oral glucose tolerance curve was normal. The diagnosis of a nutritional disturbance was not established prior to roentgenological studies. These 3 cases are reported.

Kagan, Helen, and Hirsh, W.; Toxic diarrhea among infants during the siege of Jerusalem in Summer 1948, Ann. pediat. 172: 344-351, May-June 1949.

(From Pediatric Department, Bicur Holim Hospital, Jerusalem.)

The situation before the siege, and conditions during the siege are described. The cases received are classified, giving descriptions of the symptoms, pathogensis, and therapy. Chemotherapy which had been previously successful did not work during the summer of 1948. The authors suggest that the diarrhea may have been caused by a special strain or virus resistant to sulfa and penicillin, that treat-

ment may have been started too late owing to the constant shelling which prevented bringing the sick infants to the doctor in time, or that the acute disease had been advanced by a period of hunger, malnutrition, and lack of hygiene. Most of the patients had been in a dystrophic or atrophic stage. Cell tissues, liver had suffered severe damage before the toxic diarrhea started.

Despert, J. Louise: Sleep in pre-school children: a preliminary study, Nerv. Child. 8: 8-27, Jan. 1949. (From New York Hospital and Department of Psychiatry, Cornell Medical College, New York.)

A limited number of observations on sleep in a group of 58 children of nursery school age, whose family history, development, and behavior were grossly normal and representative of a given socio-economic level, are presented.

Sperling, Melitta: Neurotic sleep disturbances in children, Nerv. Child. 8: 28-46, Jan. 1949.

Types of sleep disturbance observed, are described and discussed. Illustrative cases are cited. The types of disturbances include those based on purely psychical reasons in infants, the nightmare and night-terror, the oepidal phase, sleep-walking, psychosomatic disturbance with sudden awakening of the sleeper, sleep phobia, and insomnia of the depressive states.

Buhler, Charlotte, and **Greenberg, Mirrella:** Emotional sleep disturbances in childhood, Nerv. Child. 8: 47-49, Jan. 1949.

Emotional sleep disturbances of childhood are expressed by a set of symptoms, some of which are mutually substitutive in function. These are discussed and illustrative cases are cited. The authors emphasize the importance of ruling out a possible organic factor in instances of emotional sleep disturbances and increased emotionality.

Hughes, Elizabeth K.: Clinical observations on poliomyelitis. A review of cases admitted to the Auckland Hospital, New Zealand M. J. 48: 32-40, Feb. 1949.

In a series of 250 cases of poliomyelitis admitted over a period of 10 months, 33% were adults (over 16 years) and 67% were children. The percentage mortality rate among hospital cases, as well as the total number of deaths, was higher in the higher age groups (14% for adults, 6.3% for children 10-15 years, 1.5% for 6-10 years, no deaths below 6 years). The percentage of cases with severe residual weakness and disability was increased in the older groups. The severity of the disease appeared to decline markedly after the first 10 weeks of the epidemic. In 43% of patients muscle spasm occurred without paralysis. Muscle spasm was responsible for much acute pain and distress during the early stages of the illness and for most of the incipient deformities. Certain common virus diseases (influenza, chicken pox, and the common cold) appeared to be responsible for precipitating or unmasking a latent poliomyelitis infection and for causing an exacerbation of spasm in the convalescent patient. The problems of immunity and quarantine are discussed with the author's suggestions on the subject. The most efficient means of achieving relief and release of muscle spasm was found to be moist heat as properly applied Kenny packs at first, and later hot baths combined with suitable passive and active strengthening exercises.

Deem, Helen: The management of the new-born, New Zealand M. J. 48: 45-49, Feb. 1949.

The latest statistics for New Zealand, indicating a new low record in European neo-natal mortality and stillbirth rate, should act as a stimulus to further efforts. In this regard precautions are recommended for safeguarding infants from infection. Accommodations for new-born babies are discussed, as well as breast feeding, artificial feeding, and medical examinations.

Ferrer, M. Irene, Harvey, R. M., Weiner, H. M., Cathcart, R. T., and Cournand, A.: Hemodynamic studies in two cases of Wolff-Parkinson-White syndrome with paroxysmal AV nodal tachycardia, Am. J. Med. 6: 725-733, June 1949.

(From Cardio-Pulmonary Laboratory, Chest Service, and First Medical Service, Columbia University Division, Bellevue Hospital, New York, and Department of Medicine, College of Physicians and Surgeons, Columbia University.)

Using the right heart catheterization technique, intracardiac and peripheral arterial and venous pressure tracings were recorded simultaneously with the electrocardiogram in two patients with Wolff-Parkinson-White syndrome. Cardiac output, peripheral resistance, and stroke volume were also measured. These data were obtained during the anomalous atrioventricular conduction and also during an attack of supraventricular tachycardia in each of the two patients.

The information obtained in these two patients suggests that the anomalous conduction pathway was located on different sides of the heart in each patient and that ventricular excitation was not normal in either ventricle during aberrant conduction.

Israel, H. L., Webster, Marie B., and **Maher, Irene E.:** Clinical value of serum polysaccharide determinations by the tryptophane-perchloric acid reaction, Am. J. Med. 6: 745-750, June 1949.

(From Department of Medicine, Woman's Medical College of Pennsylvania, and Philadelphia General Hospital.)

Seibert's modification of the tryptophane-perchloric acid reaction was used to determine serum polysaccharide levels in a survey of general hospital patients. Elevation of the serum polysaccharides was most marked and frequent in patients with neoplasms, chronic infections, hyperthyroidism, and cardiovascular diseases. Abnormal values were less often observed in patients with acute infections, hepatic disease, rheumatic fever, and miscellaneous disorders. Normal values were the rule in pregnancy. Serum polysaccharide elevation appears to reflect biochemical changes different from those measured by sedimentation rate and other routine laboratory studies.

Roh, C. E., Greene, D. G., Himmelstein, A., Humphreys, G. H., III, and **Baldwin, Eleanor De F.:** Cardiopulmonary function studies in a patient with ligation of the left pulmonary artery, Am. J. Med. 6: 795-798, June 1949.

(From Departments of Medicine and Surgery, College of Physicians and Surgeons, Columbia University, and Cardio-Respiratory Laboratory, Presbyterian Hospital, New York.)

A case is reported in which cardiopulmonary function studies were performed on a patient two years after the left pulmonary artery was ligated. Cardiac catheterization revealed normal pressures in the pulmonary artery as well as in the chambers of the right side of the heart. The results of pulmonary function tests were almost completely within normal limits. The only abnormalities found were a slight increase in cardiac index and hyperventilation under all conditions of observation. However, bronchospirometry disclosed a marked limitation of gas exchange in the left lung, with carbon dioxide output limited to a lesser degree than oxygen consumption. These findings are consistent with the assumption

that anastomoses from the bronchial artery result in a considerable blood flow through the pulmonary capillary bed of the left lung.

Kern, R. A., Soloff, L. A., Snape, W. J., and **Bello, Carmen T.:** Pericardial effusion: a constant, early and major factor in the cardiac syndrome of hypothyroidism (myxedema heart), Am. J. M. Sc. 217: 609-618, June 1949.

(From Medical Service, Temple University Hospital, and Department of Medicine, Temple University School of Medicine, Philadelphia.)

"Myxedema heart," not of uncommon occurrence in untreated myxedema, has heretofore been explained on the basis of a uniform dilatation of all cardiac chambers and little consideration has been given to pericardial effusion. To date this has been reported in only 21 cases, yet the authors have demonstrated considerable pericardial effusion in 4 consecutive cases, even when the roentgenologic findings were not suggestive of its presence and there was absence of any evidence of congestive failure. In all 4 patients the effusion cleared up under thyroid medication. The authors believe that pericardial effusion is a constant, an early, and the major factor in the cardiac findings in myxedema ("myxedema heart"). "Myxedema heart" is not a cardiac disease, but a manifestation of the myxedema and has the much more favorable therapeutic and and prognostic outlook of the latter. The nature of pericardial effusion is described and the limitations of diagnostic criteria are briefly discussed.

Beelar, Virginia P., Zimmerman, H. J., and Manchester, B.: Prozone phenomenon in the serodiagnosis of syphilis. A clinical study, Am. J. M. Sc. 217: 658-665, June 1949.

(From George Washington University Medical Division, Gallinger Municipal Hospital, and Department of Medicine, George Washington University School of Medicine.)

Five cases of late syphilis with the prozone phenomenon are reported. On the basis of these cases and the investigation of others in this field, the to any particular form or stage of syphilis, occurring authors conclude that due to the prozone phenomenon, negative or doubtfully positive serologic tests do not exclude the presence of late active syphilis. The prozone phenomenon is not restricted in active and latent syphilis, in congenital or acquired forms, in central nervous system, skin, and other types of involvement, but has never been reported in primary syphilis. It is not an uncommon cause of negative serologic tests in cardiovascular syphilis.

Riley, Kathleen A.: Monilial infection of the thumb nail: Report of a case, Arch. Dermat. & Syph. 59: 589-590, May 1949.

(From Division of Dermatology and syphilology, Department of Medicine, Duke University School of Medicine, Durham, N. C.)

The case reported is of a 4-year-old child who had an infection of the left thumb nail with C. albicans. The case is interesting because of the unusual source of the infection. The child was a thumb sucker and had acquired his infection while he had a monilial infection of the mouth.

Stewart, Alice, and Hughes, J. P. W.: Tuberculosis in industry: an epidemiological study. Preliminary report, Brit. M. J. 1: 926-929, May 28, 1949.

(From Institute of Social Medicine, Oxford.)

An investigation was made in Northamptonshire in which radiography records and other statistics were explored. Though incomplete as yet, the findings to date suggest that the death rate from pulmonary tuberculosis in the shoe industry, which is high compared with all occupied and retired males, but not much higher than other industrial communities, is due partly to selective recruitment and partly to working conditions. There seem to be three aspects to selective recruitment: first, boot and shoe factories employ more men with chronic pulmonary tuberculosis than most other trades; secondly, the physique of the men is slightly subnormal; and thirdly, there is a strong family tradition in the shoe trade, so that the workers are often interrelated. There is no evidence of a specific industrial hazard, the death rate for diseases other than tuberculosis being below average. The incidence of active tuberculosis is not uniformly distributed, men and women employed in factories with large workshops contracting the disease more often than those who work in factories with small workshops. This is also the case in the clothing industry, so that the size of the working unit may prove to be an important factor in determining disease incidence in any occupation.

Morrison, L. F., Hopp, E. S., and **Wu, Rosalin:** Diagnosis of malignancy of the nasopharynx. Cytological studies by the smear technic, Ann. Otol, Rhin. & Laryng. 58: 18-32, March 1949.

(From Department of Otorhinolaryngology, Division of Surgery, University of California Medical School, San Francisco.)

The results obtained by the smear technique are excellent, but it is not a substitute for biopsy. It is an excellent adjunct in the diagnosis of exfoliating neoplasms and has shown itself to be so reliable that a positive smear demands the finding of the source of the malignant cells. A knowledge of the normal cytology of the area is a prerequisite that cannot be evaded. This method is a time consuming procedure that demands meticulous attention to detail and this is one reason why it will not become a routine laboratory procedure on a level with blood counts and urinalysis. Accurate diagnosis can only be made by a cytologist familiar with the area. A well trained technician can be used to screen out the unquestionable slides. The method has nothing to offer the casual observer.

Bensley, Sylvia H.: Some difficulties encountered in histological staining, Canad. J. M. Technol. 11: 47-52, June 1949.

(From Department of Anatomy, University of Toronto, Ontario.)

Histological staining is and probably will continue to be an empirical art rather than an exact science. Repeated efforts, careful following of directions and experience, will finally bring the rich rewards of achievemment intrinsic in any art. The various types of stains, the difficulties encountered are briefly discussed.

Russell, Helen: An essay on the reactions of the mesenchyme with especial reference to the "reticuloses", Edinburgh M. J. 56: 62-67, Feb. 1949.

(From Christie Hospital and Holt Radium Institute, Manchester.)

The subject is discussed from a historical point of view, giving the general evolution of ideas concerning the "reticuloses". The author concludes that while the discussions which have arisen round the "reticuloses" have been stimulating, particularly to the pathologist, it is doubtful whether any advance is made by using a new term to cover the more obscure mesenchymal reactions, especially as there is no indication whatever that the new name has any etiological connotation or significance.

Journal of the
AMERICAN MEDICAL WOMEN'S ASSOCIATION

INTERNATIONAL SECTION

MEDICAL WOMEN'S INTERNATIONAL ASSOCIATION

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THE COUNCIL MEETING—JULY, 1949

OFFICIALLY the Council Meeting took place in Finland, at Hameenlinna, July 18 to 21, 1949, but en route to the meeting delegates were entertained by the women physicians of Denmark and Sweden. Programs combining social activities and scientific meetings in a most agreeable and hospitable manner had been carefully planned.

In Copenhagen the program, under the direction of Dr. Borgheld Anderson, began on the afternoon of July 12, when visits were made to some of the well known Danish institutions: the Municipal Tuberculosis Clinic, the Finsen Institute, and the Gentofte County Hospital. That evening, following dinners given for groups at private homes, we were welcomed by Dr. Braestrup, Dr. Heise, and the Danish Medical Women's Club at a reception in the Domus Medica—a new building replacing the Medical Society's original home which had been destroyed in the war. The spacious reception rooms and library were very attractive; we were particularly interested in the room which had been furnished as a gift of the physicians of Sweden.

At the Danish Red Cross building the following morning Dr. Esther Ammundsen lectured on the tuberculosis problem in Europe and efforts to control spread of this disease. The International Tuberculosis Campaign was formed by Norway, Sweden, Denmark, and Finland in cooperation with UNICEEF following the original work by the Danish Red Cross in Poland. Dr. Ammundsen, Personnel Director of the International Tuberculosis Campaign, described the Tuberculin Testing and BCG Vaccination programs in progress. In one and one-half years, thirty million people have been tested and between six and seven million have been vaccinated. All the vaccine used in Europe has been sent from the Serum Institute of Copenhagen. The progress being made in Poland and other areas was then outlined. It was a most interesting report, an account of which Dr. Ammundsen, we are happy to announce, will shortly publish in this JOURNAL.

After this lecture we were guests at luncheon at the Museum of Applied Art, formerly the Frederiks Hospital, and then went to the Surgical Amphitheatre, where Dr. Van Hoosen gave the Elizabeth Blackwell Memorial Lecture, (page 484) in commemoration of the one-hundredth anniversary of the graduation of the First Woman Doctor. For an hour everyone listened with great interest to Dr. Van Hoosen's analysis of the character of Elizabeth Blackwell. Her vivid description of the difficulties, disappointments, sacrifices, and victories which Elizabeth Blackwell experienced made a profound impression upon us all.

Miss Martindale beautifully expressed to Dr. Van Hoosen appreciation of all the listeners for the stimulating story of this remarkable woman—in whose honor we were then assembled. After the address we visited the Museum of Medical His-

tory, and then we had a delightful boat ride around the harbor. In the evening we were taken to the Tivoli, world famous playground of Copenhagen. Following a beautifully cooked, meticulously served, and greatly enjoyed dinner at the Wivex, we wandered through the Tivoli, a park of 20 acres in the heart of the city, with gay dancing pavilions, beautiful gardens, restaurants, and amusements.

The next day was also filled with activity, a varied and well balanced diet of sightseeing, science, and scenery. Our first stop was the "Trollesminde," State Research Farm where experiments on breeding of cattle, horses, fur-bearing and other animals are being carried on. Then we were taken through the beautiful Danish countryside to the Central Hospital of Hillerod. It was a charming trip over a country of rolling hills and fertile pastures, through forests of beech, along lakes and rivers, past farmhouses of white stucco and red beams, with sloping roofs of red tiles or of thatch and windows filled with gay blooms of flowering plants.

At the Central Hospital of Hillerod we found sanitation combined with glamour; immaculate rooms had cheerful curtains at the windows, and hanging baskets of graceful green vines and flowering plants lined the corridors. In all the Scandinavian countries we envied the readiness with which plants grew inside the houses—frequently in pots on walls farthest from the windows, the vines trained to grow gracefully around doors and picture frames and across walls. A delicious lunch, topped off with strawberry porridge dessert, was served by the hospital.

We left the hospital in private cars supplied by the Danish women to visit several of the castles in the famed North Zealand-Frederiksborg, which houses the National Historical Museum; Fredensborg, the summer residence of the King and Queen; Kronborg, known the world over as the scene of the tragedy of *Hamlet*. After tea at Hornback, and a ride back to Copenhagen along the North Shore in late twilight, we reached the city just in time to gather up bags and souvenirs and hurry for the train to Stockholm.

The night train to Stockholm is ferried over the sea to Malmo so that passengers need not change on the combined sea-land trip. We awakened in the morning in a different region, the forests were now white birch and green pines; the houses larger in size, built of wood, and usually painted red.

In Stockholm we were met by our Swedish colleagues and assigned to our hotels, after which we reassembled at the quarters of the Swedish Medical Association where Dr. Hjerdis Nillson provided us with the program for our two days in Stockholm. The first evening we were guests of Karnbolaget for dinner at the Restaurant Hasselbacken, in Djurgarden. Karnbolaget is a firm which specializes in biochemical products, including penicillin. About 85 guests were present.

The following morning we visited the Sodersjukhuset, the Municipal Hospital, and were quite overwhelmed at the spacious corridors, elaborate equipment, and attractive accommodations for patients. Again we marvelled at the myrid of beautiful plants in the patients' rooms and solaria, the pastel colored walls, light wood furniture, and indirect lighting. We learned that the patient, if able, pays 4½ kroner a day, but that the cost is about 25 and 35 kroner, the state making up the deficit. From the Sodersjukhuset we went to the other side of Stockholm to the Karolinska Sjukhuset where Professor Nanna Svartz lectured on, "A New Serologic Test in Rheumatoid Arthritis." This was a very important contribution to research on this complex disease (Professor Svartz is sending a report of her work for publication in this JOURNAL). After the lecture we were taken on a tour through the various buildings of the hospital, all recently built, some still in process of construction. We visited also King Gustaf V's Forsknings Institute—built with money raised as a gift to the King on his 80th birthday. Luncheon was served in the Doctors Dining Room, an attractive room, the ceiling of which was particularly interesting, with murals of various medicinal herbs, flowers, and leaves, painted on the panels between the beams of pine.

We travelled by tram to Haga, the charming summer cottage of King Gustavus III, walked through the forest to the lake and took a launch to Lindingo. Here we climbed a high hill to the Millesgarden, the studio of Carl Milles, where his sculpture is exhibited in a setting of fountains, waterpools, and formal gardens. Then back to the waiting busses and into the country to the summer home of Dr. Schoultz. This was a chalet in the forest at the head of a lake, with a wonderful view of blue sky, green forests, and blue lake, the colors changing to violet hues in the long summer evening. A bountiful supper was served, the smorgasbord table groaning with its spread of delicacies.

It was late when we left and we walked several miles through the forest to the waiting busses which took us back to Stockholm.

ADA CHREE REID, M.D.

(To be concluded in December)

Journal of the
AMERICAN MEDICAL WOMEN'S ASSOCIATION

ASSOCIATION NEWS AND ANNOUNCEMENTS

PRESIDENT'S MESSAGE

In November it seems appropriate to remind you that three years ago one of your staunchest members died and a memorial was planned in her memory, the Alice Stone Woolley Memorial Lectureship. The response to this was immediate and gratifying, but we are still far short of our goal. The advantage of this particular form of memorial is that it will serve as a continuing source of stimulus to each of us in so far as we participate in our annual meetings.

As you know, the income from the fund is to provide an honorarium to a guest speaker who exemplifies outstanding ability as a woman physician in some field of medical endeavor. Also it gives us an opportunity to express our pride in the attainment of women physicians. How easy it is to take such things for granted!

Some of our members have continued to subscribe on a yearly basis. If more would do so the fund would not remain sterile.

Local branches of our association often become stagnant because of a lack of leadership and vision which would justify their existence. The dynamic groups, on the other hand, find plenty to interest them and they show it in the animation of their members.

Some of these branches have contributed to the Woolley Memorial on a group basis. Your committee, under the chairmanship of Dr. Theresa Scanlan, would appreciate a contribution from every branch each year until the fund is completed. Don't let your local dues remain sterile. Don't let other groups or individuals pay for what you will ultimately share in. If you are only mildly interested in your group, look at its accomplishments and then help it to do something worth while. Your interest will be in proportion to your participation, and this applies on a national as well as a local level.

In September I had the privilege of meeting with some of the Denver group through the enthusiastic help of Dr. Helen Maytum. Non-members present were quick to see that your association has something to offer. It is regrettable that so many of the younger medical women isolate themselves from contact with an association that is earnestly working for their interests. Concrete examples of this, such as the Woolley Lectureship, the Scholarship fund, and more relevant still, the attempt to create better opportunities for residency training, should be explained to them. The leaders in each branch should acquaint themselves with these constructive forces leading to the advancement of women physicians and make it their obligation to inform the younger women, whose attitude is due to two things: an ignorance of our value to them and a certain measure of personal insecurity which makes them afraid to adhere to what they incorrectly label a "feminist" group. They should heed the remark of a prominent medical man who said to me: "All women physicians should belong to your group." That remark should put a quietus on fears that the men will laugh at them. No thinking man or woman questions the reasonableness of subgroups in the medical profession, such as the Academy of Pediatrics. It is established to develop the resources and fill the needs of a minority group in the over-all pattern. Our group does the same and can do it well if it has the degree of support and loyalty from the women that our male colleagues obviously believe it should have. They are not laughing at us, but applauding our efforts at organization in the interests of the profession as a whole. Each woman who is better trained because of our efforts or who learns through the A. M. W. A. how to co-operate in a group is a greater asset to the medical profession.

Dorothy Wells Atkinson

Dorothy W. Atkinson, M.D.
President

Opportunities for Women in Medicine

RESIDENCIES AVAILABLE

At New England Hospital for Women and Children, Columbus Avenue and Dimock Street, Boston, there are four residencies open: Surgery—3 year approval; Pediatrics—2 years; Obstetrics—1 year; Anesthesia—1 year.

At Women and Children's Hospital, 1600 Maypole Street, Chicago, Ill., residencies are available in Surgery, Obstetrics, and Gynecology.

Starting July 1 of each year, there will be 6 residencies open to women in Houston, Texas, hospitals as follows: Internal Medicine, Jefferson Davis Hospital and Methodist Hospital; Ophthalmology, Jefferson Davis Hospital and Hermann Hospital; and Pediatrics, Jefferson Davis Hospital and Hermann Hospital. Applications should be made to the department head one year in advance.

* * *

VETERAN'S HOSPITAL INTERNSHIPS AND RESIDENCIES

A survey is being made of the various Veterans Hospitals, on internships and residencies available for women physicians. Favorable answers will appear in the JOURNAL. Here are extracts from two:

> . . . The appointment of interns and residents at this hospital is made by the Dean's Committee of the Medical College of Virginia, Richmond, Virginia. Dr. Harvey B. Haag is Chairman of this Committee, and I refer you to him for further information. If you have any women physicians who are desirous of entering the Veterans Administration on a full-time basis, it is possible that we may be able to employ two or three. . . .
>
> LESLIE H. WRIGHT, M.D., *Manager, Veterans Administration Hospital,* Richmond 19, Virginia

* * *

> . . . Concerning the placement of women physicians in this hospital, we have been approved for Residencies in General Surgery, Medicine, Radiology, Anesthesiology, Pathology, Clinical Laboratory, and Orthopedics. Residents for 1950 have not been selected yet; this will be accomplished on or about January 1, 1950. Should any member of your Association desire to make application for any of the specialties listed, the regular form utilized for Veterans Administration should be submitted to this hospital. . . .
>
> E. H. HARE, M.D., *Veterans Administration Hospital,* Indianapolis 22, Indiana

EXCHANGE FELLOWSHIPS IN OPHTHALMOLOGY

Officers of the Pan-American Association of Ophthalmology are making every effort to reorganize and expand the program of exchange fellowships, so well launched before the war. There will be a later official statement in this regard. In the meantime, there is word from Dr. Moacyr E. Alvaro, of Sao Paulo, Brazil, that there is an opportunity for a properly credited man, experienced in research, to come to Sao Paulo and do investigative work at the Escola Paulista de Medicina. The offer is for a one-year period, and possibly might be extended to two years. Room and board, and facilities for doing the work would be available, but traveling expenses cannot be furnished. Anyone interested may communicate directly with Dr. Moacyr Alvaro, Rua Consolacao 1151, Sao Paulo, Brazil. (Dr. Alvaro writes that this fellowship is open to women.—Ed.)

* * *

FELLOWSHIPS IN CARDIOVASCULAR RESEARCH

Applications for 1950 grants in aid of cardiovascular research, made available by the Life Insurance Medical Research Fund, will be received up to January. It is expected that about $550,000 will be awarded for this work. The fund will furnish support for physiological, biochemical, and pathological research bearing on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research.

At least 12 postgraduate fellowships for training in research in 1950-51 will also be granted by this Fund. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.), or the equivalent is required. The annual stipend varies, as a rule being between $3,000 and $4,000, with larger amounts in special cases. Applications will be received up to January 1, 1950. New grants and fellowships become available on July 1, 1950.

A number of pre-doctoral fellowships for basic training in research are awarded by the Fund once a year. Details will be sent upon request.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd Street, New York 29, New York.

MEDICAL OFFICERS
U. S. Public Health Service

A competitive examination for appointment of Medical Officers in the Regular Corps of the United States Public Health Service will be held on January 9, 10, and 11, 1950. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to homes of candidates. Applications must be received *no later than December 12, 1949.*

The Regular Corps is a commissioned officer corps composed of members of various medical and scientific professions, appointed in appropriate professional categories such as medicine, dentistry, nursing, engineering, pharmacy, etc. All commissioned officers are appointed to the general service and are subject to change of station.

Appointments will be made in the grades of Assistant Surgeon (1st Lt.) and Senior Assistant Surgeon (Captain). Appointments are permanent and provide opportunities to qualified physicians for a life time career in clinical medicine, research, and public health.

Requirements for appointment in the grade of Assistant Surgeon: the applicant must be a citizen of the United States, at least 21 years of age, and a graduate from a recognized school of medicine. Physicians who are successful in the examination and are now serving internships will not be placed on active duty in the Regular Corps until completion of internships. Applicants for appointment in the grade of Senior Assistant Surgeon must meet the above requirements and must have had a total of at least ten years of educational training and professional experience subsequent to high school. The entrance examination will include written professional tests, an oral interview, and a physical examination.

The professional written examination for the grade of Assistant Surgeon will cover the following subjects: (1) anatomy, physiology, biochemistry; (2) materia medica and therapeutics; (3) obstetrics and gynecology; (4) practice of surgery; (5) practice of medicine; (6) epidemiology and hygiene; (7) pathology and bacteriology. Senior Assistant Surgeon applicants will be examined on subjects 4, 5, 6, and 7 listed above.

Gross pay is governed by the Career Compensation Act of 1949, and is identical to that of officers of equivalent rank in the Army and Navy. Under current law, entrance pay for an Assistant Surgeon with dependents is $5,686.56 per annum; for Senior Assistant Surgeon with dependents, $6,546. These figures include the $1,200 annual additional pay received by medical officers as well as subsistence and rental allowance.

Promotions. Provisions are made for promotion at regular intervals up to and including the grade of Senior Surgeon (Lt. Col.) and for selection for promotion to the grade of Medical Director (Col.)

Retirement pay after 30 years of service or at the age of 64, is three-fourths of annual base pay at the time of retirement. Retirement for disability is authorized under the Career Compensation Act and disability retirement pay is at a minimum, one-half of the annual base pay at the time of retirement.

Additional benefits include 30 days annual leave, sick leave, full medical care, and many of the usual privileges extended to members of the military forces.

Application forms and additional information may be obtained by writing to the Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C. Attention: Division of Commissioned Officers. *Applications received after December 12, 1949, will not be accepted for this examination,* but will be admitted to the examination in May, 1950.

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FELLOWSHIPS IN EXFOLIATIVE CYTOLOGY

The American Cancer Society announces a series of fellowships available in various laboratories, including grants to the institutions as well as to individuals. In New York City there are six fellowships available at Cornell University Medical College, and one at the New York Post-Graduate Hospital. Individual applicants for fellowships should apply directly to the institutions—Dr. George N. Papanicolaou, at Cornell, and Dr. Locke L. Mackenzie, at Post-Graduate.

* * *

AIR FORCE MEDICAL RESERVE

General Hoyt S. Vandenberg, Chief of Staff, U. S. Air Force, recently announced that applications are being received for commissions in the newly created Air Force Medical Reserve. Physicians, dentists, nurses and other medical personnel who served with the Army Air Forces during the war may make application through the Air Adjutant General, U. S. Air Force, in Washington.

* * *

MAYO FOUNDATION, ROCHESTER, MINNESOTA

Graduate Courses in surgery and medicine are open to anyone fulfilling the requirements. Applications should be made at least a year in advance.

After three years of training in a special subject and an acceptable thesis, a Master of Science degree is received from the University of Minnesota.

VIRGINIA MERIWETHER DAVIES, M.D.

DR. VIRGINIA MERIWETHER DAVIES, a notable woman physician, died at her home in Congers, New York, April 21, 1949, three days following her eighty-seventh birthday. Dr. Davies' record of service is remarkable; a history of her life reads like a story of adventure and romance. From press clippings, and from personal accounts given us by Dr. Davies' cousin, the celebrated Dorothy Dix of New Orleans, we glean the facts of her career.

Virginia Meriwether Davies, M.D.

Dr. Davies was of distinguished ancestry. Her father was Miles Meriwether, a prominent engineer of the city of Memphis, Tennessee, and credited with the lion's share of reconstruction in that city after the Civil War. Her mother, Lide Smith, although a Southerner, was an Abolitionist and a friend of Lucy Stone. Meriwether Lewis, of the Lewis and Clark expedition, and William Douglas, tutor to Presidents Jefferson, Madison, and Monroe, were among her forbears.

Virginia Meriwether received her academic education at Mary Baldwin School in Staunton, Virginia, and then entered the Medical College of New York Infirmary, where the founders, Emily and Elizabeth Blackwell, were her teachers. After receiving her medical degree in 1886, she remained with the Infirmary until 1892. Then she married the famous painter, Arthur Davies, and they settled on their farm in Rockland County, which became a rendezvous for artists and writers. Dr. Davies had planned to devote her time to the cultivation of farm produce but her professional services were in such demand that she resumed practice and carried it on until three weeks before her death.

Routine practice, and the delivery of six thousand babies, was interspersed with some exciting experiences. During the terrific blizzard of 1888 in New York, Dr. Davies, with an assistant, directed crews to shovel snow from drifts, some of which were as high as seventeen feet, so that milk might be brought to babies in the New York Infirmary where she was head resident physician. Accidents at the stone quarries and industrial plants near her farm in Rockland County called for emergency services. Her early calls were made with horse-and-buggy, but at the age of sixty-two she acquired an automobile and drove it herself.

Because of her unusual personality and accomplishments, the work and fame of this woman spread from New York State into other States, and, although Dr. Davies experienced all the handicaps and ridicule known to pioneer women physicians in her early career, she lived to enjoy wide recognition of her achievements. In recent years she was honored by many organizations and participated in various radio programs. She was especially interested in the culture of vegetables and the planting of orchards and was as conversant with the field of botany as with that of medicine. During the recent war the Office of War Information published a pamphlet on the activities of Dr. Davies' farm which is now operated by her son, Niles M. Davies.

And now those of us who like family tradition will be pleased to know that the Davies name is to be found again this year on the roster of students entering the field, for Silvia Ann Davies, one of Dr. Davies' five grandchildren has started her studies at Columbia University College of Physicians and Surgeons. May she follow in the footsteps of her renowned grandmother, a great woman and a distinguished physician.

ELIZABETH BASS, M.D.

News of Women in Medicine

DR. ANTOINETTE LE MARQUIS, chief of the medical staff of Guadalupe Clinic, announced in April the opening of a new cancer detection center for well women.

Guadalupe Clinic located in the Logan Heights District of San Diego, California, serves annually about 6,000 patients. Dr. Le Marquis, head of the clinic this year, is the first woman physician to be so honored. The Clinic began modestly in 1945 in the back rooms of Our Lady of Guadalupe Church on Kearney Street. It grew rapidly and in 1948 a building was erected. The patients pay according to their means, but the financing of the major part of the project is borne by the Catholic Diocese of San Diego and the Community Chest.

Dr. Le Marquis' new cancer detection clinic adds one more to the chain of such clinics which have been started across the country. The first was established in 1937 at the Infirmary for Women and Children in New York City by Dr. Elise L'Esperance. Later Dr. Catherine Macfarlane in Philadelphia, Dr. Augusta Webster in Chicago, Dr. Mary Margaret Frazer in Detroit, and Dr. Elizabeth Mason Hohl in Los Angeles were responsible for the opening of similar clinics. Many thousands of patients have been assured of freedom from cancer, and hundreds of lives have been saved. Since its opening in 1945, 18,000 patients have been examined in the clinic in the Los Angeles Center alone.

* * *

Navy hospitals have been assigned women interns for the first time. Those receiving appointments were LIEUT. (j.g.) SUZANNE W. BROWN, graduate of the Medical College of Virginia, to the Naval Hospital, National Naval Medical Center, Bethesda, Md.; LIEUT. (j.g.) MARY W. TILDEN, also a graduate of the Medical College of Virginia, to the Naval Hospital, Great Lakes, Ill.; and LIEUT. (j.g.) HANNAH H. PENDERGAST, graduate of Vermont University School of Medicine, to the Naval Hospital, Chelsea, Massachusetts.

Seventeen other women who have recently obtained medical degrees have been assigned to civilian hospitals under the Navy's Civilian Intern Training Program.

* * *

DR. CAROL PRYOR has been named college physician at the Georgia State College for Women at Milledgeville, Georgia.

ANTOINETTE LEMARQUIS, M.D.

DR. MARIE PICHEL WARNER, of New York City, was recently appointed an Adjunct in Gynecology on the Medical Board of the Hillside Hospital in Bellerose, Long Island.

* * *

DR. GRACE GOLDSMITH, of Tulane University, has been awarded a grant-in-aid for $30,132 by the Nutrition Foundation for continued research in the vitamin B group.

* * *

At a Symposium of the Fulton County Medical Society in Atlanta, Georgia, DR. MARY GILLILAND spoke on *The Relationship of Maternal RH—Antibody Titers to the Occurrence and Prognosis of Erythroblastosis.*

* * *

DR. LAURETTA KRESS and her husband, Dr. Daniel Kress, celebrated their 65th wedding anniversary July 9th in Orlando, Florida. The couple graduated from the University of Michigan in 1884. They assisted in establishing the Washington Sanitarium in Washington, D. C., the Seventh Day Adventist Sanitarium in England, and a hospital in Australia. Dr. Lauretta Kress is an obstetrician who has delivered nearly 5,000 babies, with only one maternal death.

Dr. Dora Papara of Athens has been awarded the Soroptimist Fellowship of $3,000 for study at the University of Pennsylvania. The Soroptimist International Association, numbering in its American Federation 11,000 executive and professional women throughout the United States, Canada, and South America, has set up the fellowship fund to encourage progress in distinctive, frontier fields of endeavor. In 1933, Dr. Papara was appointed by the Greek Ministry of Health as Chief of the Women's and Children's Section of the Public Lunatic Asylum of Athens. While serving there she applied, for the first time in humans, experimental tests on the effects of hypertonic and hypotonic solutions given intravenously in high doses. She was appointed to her present position as Chief of the Psychiatric Clinic of the Public Asylum in Athens in 1944. Dr. Papara will specialize in this country in the study of general neuropsychiatry, neuropsychiatry of abnormal children, and research on the hereditary possibilities in alcoholism.

Greek Doctor Matriculates at University of Pennsylvania Medical School—**Dr. Dora Papara (center), fellowship student from Athens, Greece, is welcomed to the University of Pennsylvania by Dr. John McK. Mitchell (right), Dean of the Medical School, and Dr. Marion Kolbye (left), Chairman of the Fellowship Awards Committee of the American Federation of Soroptimist Clubs, donor of the fellowship.**

Letters to the Editor

On page 348 of the August number of the JOURNAL, neither Dr. Thelander nor Dr. Baumgartner mentions the fact that New York University and Bellevue Medical College was the first medical institution to confer the degree of Doctor of Public Health, thus pointing the way to Harvard and similar universities.

I believe Dr. Baker was the first woman to receive this degree. The course was two years in length and covered quite an extensive ground. Dr. William H. Park, of the 16th St. Laboratory of the Department of Health, directed the course. I entered the class which was formed in 1916, but owing to war conditions graduation did not take place until 1921. There were four or five men in the class and only one woman. My diploma is dated June, 1921, and signed by Elmer Brown, Chancellor of the University, and Samuel Brown, Dean of the University; also Milton Eloomis, Registrar. There were at that time some—perhaps one or two—women doctors working in the laboratory who a few years later received the Dr.P.H. degree. A thesis was required from each graduate.

MAUDE GLASGOW,
M.D., *Dr.P.H.*

Thank you very much for the collection of THE JOURNAL OF THE AMERICAN MEDICAL WOMEN'S ASSOCIATION. . . . I also want to take this opportunity to tell you how much we all appreciate the magnificent use you make of our material in the JOURNAL . . . and to thank you for the very fine job you did with the July issue in connection with World Health Day.

ROBERTO RENDUELES,
Public Information Officer,
World Health Organization

* * *

A few months ago you ran a suggestion for the treatment of painful and stiff muscles (ethyl chloride). I just thought it might interest you to hear that in a large number of light cases this easily and quickly applied treatment is helping very well.

H. BURESCH, M.D., *Alabama*

Subject to the usual restrictions, we shall print letters from subscribers on any side of any subject of interest to the medical profession. THE JOURNAL OF THE AMERICAN MEDICAL WOMEN'S ASSOCIATION *often may not agree with the sentiments expressed, and disclaims any responsibility for what appears in this column.*

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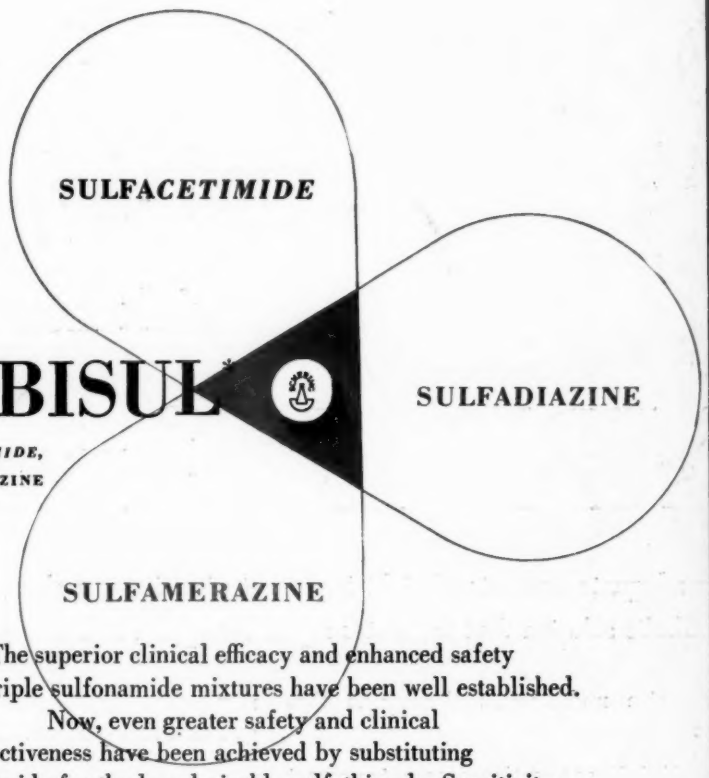

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